



BSI Standards Publication

Biological evaluation of medical devices

Part 4: Selection of tests for interactions with blood

National foreword

This British Standard is the UK implementation of EN ISO 10993-4:2017+A1:2025. It is identical to ISO 10993-4:2017, incorporating amendment 1:2025. It supersedes BS EN ISO 10993-4:2017, which is withdrawn.

The start and finish of text introduced or altered by amendment is indicated in the text by tags. Tags indicating changes to ISO text carry the number of the ISO amendment. For example, text altered by ISO amendment 1 is indicated by **A1** **A1**.

The UK participation in its preparation was entrusted to Technical Committee CH/194, Biological evaluation of medical devices.

A list of organizations represented on this committee can be obtained on request to its committee manager.

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Date	Text affected
31 March 2025	Implementation of ISO amendment 1:2025 with CEN endorsement A1:2025

English Version

Biological evaluation of medical devices - Part 4: Selection of tests for interactions with blood (ISO 10993-4:2017)

Évaluation biologique des dispositifs médicaux - Partie
4: Choix des essais pour les interactions avec le sang
(ISO 10993-4:2017)

Biologische Beurteilung von Medizinprodukten - Teil 4:
Auswahl von Prüfungen zur Wechselwirkung mit Blut
(ISO 10993-4:2017)

This European Standard was approved by CEN on 4 October 2017.

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European foreword

The text of ISO 10993-4:2017 has been prepared by Technical Committee ISO/TC 194 “Biological and clinical evaluation of medical devices” of the International Organization for Standardization (ISO) and has been taken over as EN ISO 10993-4:2017 by Technical Committee CEN/TC 206 “Biological and clinical evaluation of medical devices” the secretariat of which is held by DIN.

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of an identical text or by endorsement, at the latest by April 2018, and conflicting national standards shall be withdrawn at the latest by April 2018.

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

This document supersedes EN ISO 10993-4:2009 and EN ISO 10993-4:2017.

This document has been prepared under a mandate given to CEN by the European Commission and the European Free Trade Association, and supports essential requirements of EU Directives.

For relationship with EU Directives, see informative Annex ZA and Annex ZB, which is an integral part of this document.

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NOTE 1 The way in which these referenced documents are cited in normative requirements determines the extent (in whole or in part) to which they apply.

Table — Correlations between undated normative references and dated EN and ISO standards

Normative references as listed in Clause 2 of the ISO standard	Equivalent dated standard	
	EN	ISO or IEC
ISO 10993-1	EN ISO 10993-1:2009	ISO 10993-1:2009
ISO 10993-12	EN ISO 10993-12:2012	ISO 10993-12:2012

NOTE 2 This part of EN ISO 10993 refers to ISO 10993 1 which itself refers to ISO 14971. In Europe, it should be assumed that the reference to ISO 14971 is to EN ISO 14971:2012.

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Endorsement notice

The text of ISO 10993-4:2017 has been approved by CEN as EN ISO 10993-4:2017 without any modification.

European foreword to amendment A1

This document (EN ISO 10993-4:2017/A1:2025) has been prepared by Technical Committee ISO/TC 194 "Biological and clinical evaluation of medical devices" in collaboration with Technical Committee CEN/TC 206 "Biological and clinical evaluation of medical devices" the secretariat of which is held by DIN.

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This document has been prepared under a standardization request addressed to CEN by the European Commission. The Standing Committee of the EFTA States subsequently approves these requests for its Member States.

For the relationship with EU Legislation, see informative Annex ZA, which is an integral part of this document.

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Endorsement notice

The text of ISO 10993-4:2017/Amd 1:2025 has been approved by CEN as EN ISO 10993-4:2017/A1:2025 without any modification.

Annex ZA (informative)

Relationship between this European Standard the General Safety and Performance Requirements of Regulation (EU) 2017/745 aimed to be covered

This European standard has been prepared under M/575 to provide one voluntary means of conforming to the General Safety and Performance Requirements of Regulation (EU) 2017/745 of 5 April 2017 concerning medical devices [OJ L 117] and to system or process requirements including those relating to quality management systems, risk management, post-market surveillance systems, clinical investigations, clinical evaluation or post-market clinical follow-up.

Once this standard is cited in the Official Journal of the European Union under that Regulation, compliance with the normative clauses of this standard given in Table ZA.1 and application of the edition of the normatively referenced standards as given in Table ZA.2 confers, within the limits of the scope of this standard, a presumption of conformity with the corresponding General Safety and Performance Requirements of that Regulation, and associated EFTA Regulations.

Where a definition in this harmonised standard differs from a definition of the same term set out in Regulation (EU) 2017/745, the differences shall be indicated in the Annex Z. For the purpose of using this standard in support of the requirements set out in Regulation (EU) 2017/745, the definitions set out in this Regulation prevail.

Where the European standard is an adoption of an International Standard, the scope of this document can differ from the scope of the European Regulation that it supports. As the scope of the applicable regulatory requirements differ from nation to nation and region to region the standard can only support European regulatory requirements to the extent of the scope of the European Regulation for medical devices ((EU) 2017/745).

NOTE 1 Where a reference from a clause of this standard to the risk management process is made, the risk management process needs to be in compliance with Regulation (EU) 2017/745. This means that risks have to be 'reduced as far as possible', 'reduced to the lowest possible level', 'reduced as far as possible and appropriate', 'removed or reduced as far as possible', 'eliminated or reduced as far as possible', 'removed or minimized as far as possible', or 'minimized', according to the wording of the corresponding General Safety and Performance Requirement.

NOTE 2 The manufacturer's policy for determining **acceptable risk** must be in compliance with General Safety and Performance Requirements 1, 2, 3, 4, 5, 8, 9, 10, 11, 14, 16, 17, 18, 19, 20, 21 and 22 of the Regulation.

NOTE 3 When a General Safety and Performance Requirement does not appear in Table ZA.1, it means that it is not addressed by this European Standard.

Table ZA.1 — Correspondence between this European Standard and Annex I of Regulation (EU) 2017/745 [OJ L 117] and to system or process requirements including those relating to quality management systems, risk management, post-market surveillance systems, clinical investigations, clinical evaluation or post-market clinical follow-up

General Safety and Performance Requirements of Regulation (EU) 2017/745	Clause(s)/subclause(s) of this EN	Remarks/Notes
10.1 [(a) and (b)]	6	GSPR 10.1 [(a) and (b)] is partly covered by this document since the document does not provide requirements on design and manufacture and packaging. However, this document provides a means to assess interactions of medical devices/materials with blood. Other forms of toxicity and flammability are not covered.
10.2	6	GSPR 10.2 is partly covered by this document since the document does not provide requirements on design and manufacture. However, this document provides a means to assess interactions of contaminants and residues from medical devices/materials with blood.
10.4.1 (first paragraph)	6	GSPR 10.4.1 (first paragraph) is partly covered by this document since the document does not provide requirements on design and manufacture. However, this document provides a means to assess interactions of medical devices/materials with blood. Other forms of toxicity are not covered.

Table ZA.2 — Normative references from Clause 2 of this document and their corresponding European publications

Column 1 Reference in Clause 2	Column 2 International Standard Edition	Column 3 Title	Column 4 Corresponding European Standard Edition
ISO 10993-1	ISO 10993-1:2018	Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process	EN ISO 10993-1:2020
ISO 10993-12	ISO 10993-12:2021	Biological evaluation of medical devices — Part 12: Sample preparation and reference materials	EN ISO 10993-12:2021

The documents listed in the Column 1 of Table ZA.2, in whole or in part, are normatively referenced in this document, i.e., are indispensable for its application. The achievement of the presumption of conformity is subject to the application of the edition of Standards as listed in Column 4 or, if no European Standard Edition exists, the International Standard Edition given in Column 2 of Table ZA.2.

WARNING 1 Presumption of conformity stays valid only as long as a reference to this European standard is maintained in the list published in the Official Journal of the European Union. Users of this standard should consult frequently the latest list published in the Official Journal of the European Union.

WARNING 2 Other Union legislation may be applicable to the product(s) falling within the scope of this standard.

Annex ZB (informative)

Relationship between this European Standard and the essential requirements of Directive 90/385/EEC [OJ L 189] aimed to be covered

This European Standard has been prepared under a Commission's joint standardization request M/BC/CEN/89/9 concerning harmonized standards relating to horizontal aspects in the field of medical devices to provide one voluntary means of conforming to essential requirements of Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices [OJ L 189].

Once this standard is cited in the Official Journal of the European Union under that Directive, compliance with the normative clauses of this standard given in Table ZB.1 confers, within the limits of the scope of this standard, a presumption of conformity with the corresponding essential requirements of that Directive and associated EFTA regulations.

NOTE 1 Where a reference from a clause of this standard to the risk management process is made, the risk management process needs to be in compliance with Directive 90/385/EEC as amended by 2007/47/EC. This means that risks have to be reduced 'as far as possible', 'to a minimum', 'to the lowest possible level', 'minimized' or 'removed', according to the wording of the corresponding essential requirement.

NOTE 2 The manufacturer's policy for determining acceptable risk must be in compliance with Essential Requirements 1, 4, 5, 8, 9 and 10 of the Directive.

NOTE 3 This Annex ZB is based on normative references according to the table of references in the European foreword, replacing the references in the core text.

NOTE 4 When an Essential Requirement does not appear in Table ZB.1, it means that it is not addressed by this European Standard.

Table ZB.1 — Correspondence between this European Standard and Annex I of Directive 90/385/EEC [OJ L 189]

Essential Requirements of Directive 90/385/EEC	Clause(s)/subclause(s) of this EN	Remarks/Notes
9 (first indent)	6.1	ER 9 (first indent) is only partly covered by ISO 10993-4, since the standard does not provide requirements on design and manufacture. However, this part of ISO 10993 does specify test methods for the assessment of the compatibility of medical devices and materials intended for use in medical devices with blood. Other forms of toxicity are not dealt with in this standard.
9 (second indent)	6.1	ER 9 (second indent) is only partly covered by ISO 10993-4, since the standard does not provide requirements on design and manufacture. However, this standard does provide a means to evaluate the compatibility of medical devices and materials intended for use in medical devices with blood.

General Note: Presumption of conformity depends on also complying with all relevant clauses/subclauses of ISO 10993-1.

WARNING 1 — Presumption of conformity stays valid only as long as a reference to this European Standard is maintained in the list published in the Official Journal of the European Union. Users of this standard should consult frequently the latest list published in the Official Journal of the European Union.

WARNING 2 — Other Union legislation may be applicable to the products falling within the scope of this standard.

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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 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*.

This third edition cancels and replaces the second edition (ISO 10993-4:2002), which has been technically revised.

It also incorporates the Amendment ISO 10993-4:2002/Amd 1:2006.

The following changes were made:

- a) some definitions have been revised and new definitions have been added;
- b) Tables 1 and 2 have been consolidated into a single new [Table 1](#) with test categories and headers reorganized to emphasize and include material and mechanical-induced haemolysis testing and *in vitro* and *in vivo* testing for assessment of risk for thrombosis;
- c) 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) [Annex C](#) has been added to cover the topic of *in vivo* thrombosis and methods for testing;
- f) [Annex D](#), which was Annex C in the previous edition, has been updated and now includes added information on mechanically-induced haemolysis;
- g) [Annex E](#) has been added to cover the topic of complement testing and best test method practices;
- h) [Annexes F](#) and [G](#) have been added to present the less common tests used to assess interactions with blood and the tests that are not recommended for 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.

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^[14] chapters 9 and 10. This publication was subsequently revised^[15].

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.

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.

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: Evaluation and testing 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 <http://www.electropedia.org/>
- ISO Online browsing platform: available at <http://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 [A1](#) ISO/TS 10993-20 [A1](#).)

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

EXAMPLE Drug and parenteral nutrition solution delivery devices.

3.13**legally-marketed comparator device****LMCD**

approved, or cleared 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

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 a 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
MRI	magnetic resonance imaging
PET	positron emission tomography
PF-4	platelet factor 4

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 complexes
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 indirectly contacting blood

- *Text deleted*
- blood monitors with indirect blood contact;
- *Text deleted*
- devices for the storage and administration of either saline or therapeutics, or both (e.g. tubing and bags); 
- extension sets;
-  *Text deleted* 

5.2.3 External communicating devices directly contacting circulating blood

- atherectomy devices;
-  blood collection devices; 
- blood monitoring devices with direct  *Text deleted*  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, *in vivo* testing for evidence of thrombosis is frequently the preferred method for device characterization in the thrombosis category. However, in some cases, written rationales that include a combination of tests from the categories of coagulation, platelets, haematology and complement can be used as a substitute for thrombosis testing.

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. For example, for devices of defined geometry such as a vascular stent, the surface area used in the test, in cm², shall be given consideration relative to the fluid volume of the *in vitro* test system. For devices with undefined or complicated geometry (such as a dispersion of PVA particles used as an embolization agent), mass should be used instead of surface area to determine the amount of sample used in test system.

Only direct or indirect blood-contacting parts should be tested. [A1](#) For direct contact haemocompatibility testing (e.g. direct haemolysis, complement activation, coagulation, platelet activation, haematology, *in vitro* or *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. [A1](#) 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.

[A1](#) 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* or *ex vivo* thrombosis), such tests do not apply to indirect contact applications. For externally communicating medical devices or components that have indirect blood contact, only an indirect contact haemolysis test is generally recommended. [A1](#)

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[\[6\]](#).

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.

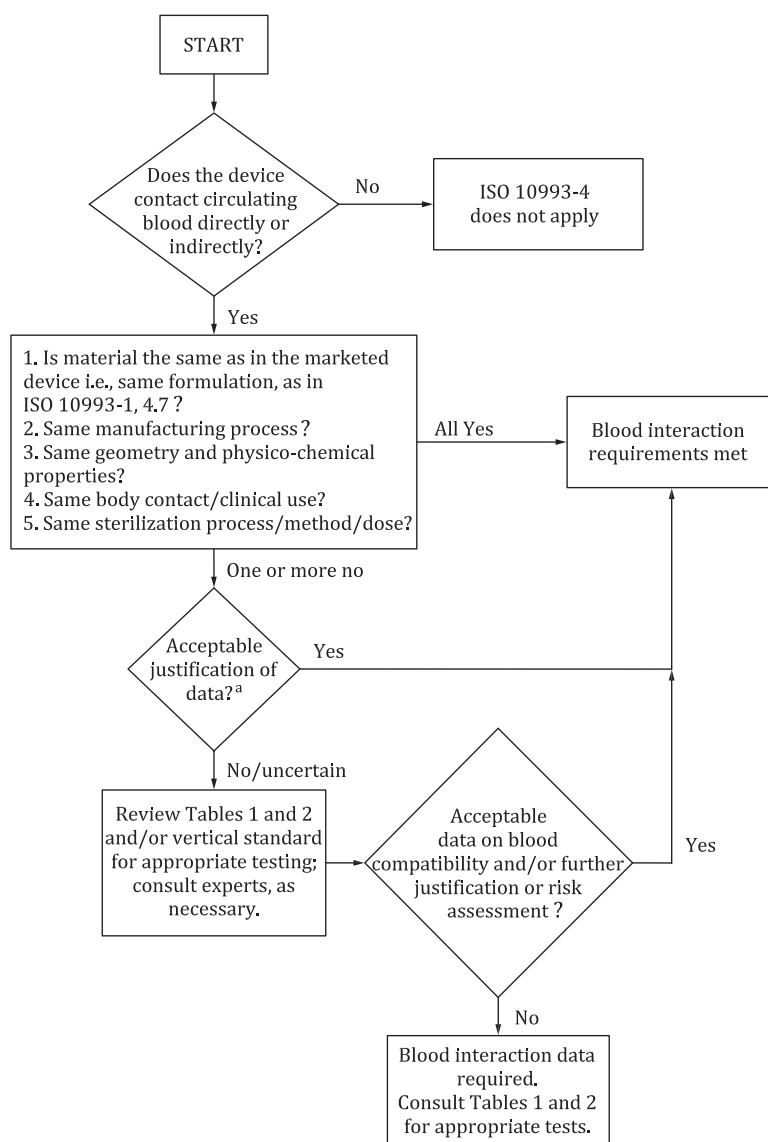
NOTE 1 [A1](#) Changes in the manufacturing process (e.g. change in manufacturer), the use of different manufacturing aids that can affect the surface properties or the chemistry of the complete sterilized device can also impact haemocompatibility. [A1](#)

NOTE 2 Where aging could impact the final device properties, use of aged samples can also be necessary. (For example, the properties of biologically active coatings such as heparin could change over time.)

6.1.5 Tests which do not simulate the conditions of a device during use may not predict accurately the nature of the blood/device interactions which can occur during clinical applications. In addition, the capacity of short-term *in vitro* or *ex vivo* tests to predict performance in actual clinical applications is thought to be higher when the clinical application involves limited exposure rather than prolonged or permanent exposure.

NOTE Simplified testing of candidate device materials (e.g. surface geometric and functional chemical modifications) can serve as a crucial step in device material identification, optimization and selection.

6.1.6 If an animal study is to be conducted, devices whose intended use is *ex vivo* (external communication) should be tested *ex vivo* and devices whose intended use is *in vivo* (implants) should be tested *in vivo* in an animal model simulating as closely as possible conditions of clinical use. Protocols in such investigations should specifically call out each test category (see [6.2.1](#)) being evaluated and describe the specific method(s) of assessment.



^a For direct and indirect contact devices, the necessity for haemocompatibility testing should be considered based upon appropriate risk analysis, including prior haemocompatibility testing, clinical data, extractable/leachable data, and/or information on surface characteristics. For example, for devices with direct contact, extractable/leachable testing may not be sufficient if the surface morphology is changed, even if the extractable/leachable chemistry is the same (see ISO 10993-1).

Figure 1 — Decision tree to help determine whether testing for interaction with blood is necessary

Table 1 — Devices or device components and categories of appropriate testing for consideration

Device examples	Test category						In vivo or ex vivo ^a
	Haemolysis		Thrombosis ^c				
	Material-induced	Mechanically-induced	Coagulation	Platelet activation	Complement ^d	Haematology	
External communicating devices indirectly contacting blood ^e							
Blood monitors with indirect blood contact	X						
Devices for storage and administration of saline and/or therapeutics (e.g. tubing and bags), extension sets	X						
External communicating devices directly contacting circulating blood ^b							
Blood collection devices	X		X	X		X	
Blood administration sets and extension sets	X	X ^f	X	X		X	
Catheters in place for less than 24 h (e.g. atherectomy devices, intravascular ultrasound catheters, antegrade or retrograde coronary perfusion catheters, guide wires), cannulae	X		X	X		X	X
Catheters in place for more than 24 h (e.g. parenteral nutrition catheters, central venous catheters); cannulae	X		X	X		X	X
Cell savers	X	X	X	X			
Devices for adsorption of specific substances from blood	X	X	X	X	X		
Donor and therapeutic aphaeresis equipment and cell separation systems	X	X	X	X	X		
Cardiopulmonary bypass system and components	X	X	X	X	X	X	X
Haemodialysis or haemofiltration equipment	X	X	X	X	X	X	X
Leukocyte removal filter	X		X	X	X	X	X
Percutaneous circulatory support devices	X	X	X	X	X	X	X
Implant devices							
Annuloplasty rings, mechanical heart valves	X	X					X
Embolization devices	X						X
Endovascular grafts	X						X
Implantable defibrillator and cardioverter leads	X						X
Intra-aortic balloon pumps	X	X					X
^a Thrombosis is an in vivo or ex vivo phenomenon but can be simulated with in vitro conditions. In vivo or ex vivo testing is not always unnecessary if clinically relevant in vitro thrombosis testing is performed.							
^b Some examples can contain other components with indirect blood contact. For device components that only have indirect blood contact, direct contact material-induced haemolysis, mechanical haemolysis, thrombosis and complement activation are not always necessary. For components with indirect blood contact, generally only an indirect contact haemolysis test is recommended.							
^c It is recognized that coagulation, platelet and leucocyte responses are primarily involved in the process of thrombosis. Therefore, in vitro thrombogenicity methods can be acceptable in place of in vivo testing if scientifically justified. The manufacturer should justify which specific testing in the coagulation, platelet and haematology test categories is appropriate for their devices.							
^d Complement activation testing is also requested by certain regulatory authorities to address other end points such as anaphylaxis for all devices with direct blood contact.							
^e Except for devices composed of novel materials, each test in the category of thrombosis is generally not necessary for indirect blood contact devices.							
^f For blood administration sets without using mechanical pumps, mechanically induced haemolysis testing is generally not necessary.							

^a Thrombosis is an in vivo or ex vivo phenomenon but can be simulated with in vitro conditions. In vivo or ex vivo testing is not always unnecessary if clinically relevant in vitro thrombosis testing is performed.

^b Some examples can contain other components with indirect blood contact. For device components that only have indirect blood contact, direct contact material-induced haemolysis, mechanical haemolysis, thrombosis and complement activation are not always necessary. For components with indirect blood contact, generally only an indirect contact haemolysis test is recommended.

^c It is recognized that coagulation, platelet and leucocyte responses are primarily involved in the process of thrombosis. Therefore, in vitro thrombogenicity methods can be acceptable in place of in vivo testing if scientifically justified. The manufacturer should justify which specific testing in the coagulation, platelet and haematology test categories is appropriate for their devices.

^d Complement activation testing is also requested by certain regulatory authorities to address other end points such as anaphylaxis for all devices with direct blood contact.

^e Except for devices composed of novel materials, each test in the category of thrombosis is generally not necessary for indirect blood contact devices.

^f For blood administration sets without using mechanical pumps, mechanically induced haemolysis testing is generally not necessary.

Table 1 (continued)

Device examples	Test category						
	Haemolysis		Thrombosis ^c				In vivo or ex vivo ^a
	Material-induced	Mechanically-induced	Coagulation	Platelet activation	In vitro	Complement ^d	
Pacemaker leads	X						X
Prosthetic (synthetic) vascular grafts and patches, including arteriovenous shunts	X						X
Stents (vascular)	X						X
Tissue heart valves, vascular grafts and patches and AV shunts	X						X
Total artificial hearts	X	X					X
Vena cava filters	X						X
Ventricular-assist devices	X	X					X

^a Thrombosis is an in vivo or ex vivo phenomenon but can be simulated with in vitro conditions. In vivo or ex vivo testing is not always unnecessary if clinically relevant in vitro thrombosis testing is performed.

^b Some examples can contain other components with indirect blood contact. For device components that only have indirect blood contact, direct contact material-induced haemolysis, thrombosis and complement activation are not always necessary. For components with indirect blood contact, generally only an indirect contact haemolysis test is recommended.

^c It is recognized that coagulation, platelet and leucocyte responses are primarily involved in the process of thrombosis. Therefore, in vitro thrombogenicity methods can be acceptable in place of in vivo testing if scientifically justified. The manufacturer should justify which specific testing in the coagulation, platelet and haematology test categories is appropriate for their devices.

^d Complement activation testing is also requested by certain regulatory authorities to address other end points such as anaphylaxis for all devices with direct blood contact.

^e Except for devices composed of novel materials, each test in the category of thrombosis is generally not necessary for indirect blood contact devices.

^f For blood administration sets without using mechanical pumps, mechanically induced haemolysis testing is generally not necessary. ⁽⁴⁾

6.1.7 *In vitro* tests are regarded as useful in screening external communicating devices or implants and potential early interactions between devices/materials with blood, but may not be accurate predictors of blood/device interactions occurring upon prolonged or repeated exposure or permanent contact (see 6.3.1).

NOTE For new devices or devices where there is a change in geometry, testing under physiologic flow can be needed. For long-term catheters or permanent implants, *in vitro* test systems might not be sufficient due to blood stability issues.

6.1.8 Devices or device components which come into very brief/transient contact with circulating blood (e.g. lancets, hypodermic needles, capillary tubes that are used for less than 1 min) generally do not require blood/device interaction testing.

NOTE 1 For products made with materials such as coatings that could be left in contact with blood after the device is removed, blood/device interaction testing might be necessary.

NOTE 2 If some device components (e.g. syringe bodies) are in contact with fluids that will ultimately be injected into the patient, and the storage time is unspecified or greater than 1 min, haemolysis testing of the fluid-contacting component would be needed, even though the device itself would be in contact with circulating blood for less than 1 min.

6.1.9 Disposable laboratory equipment used for the collection of blood and performance of *in vitro* tests on blood shall be evaluated to ascertain that there is no significant interference with the test being performed.

6.1.10 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. For devices that operate over a range of conditions, the extreme and the average conditions should be considered. However, species differences and other factors may limit the predictability of any test.

6.1.11 Because of species differences in blood reactivity, human blood should be used where possible (with the exception of established test methods with animal blood, such as some haemolysis tests). 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 shall be considered.

Blood values and reactivity in humans and non-human primates are very similar^[204]. The use of animals, such as the rabbit, pig, calf, sheep or dog, can also be acceptable for a particular type of test. However, since species differences may be significant (for example, platelet adhesion^{[148][150]}, thrombosis^[44] and haemolysis^[47] tend to occur more readily in the canine than in the human), all results of animal studies shall be interpreted with caution. The species selected and the number of animals used shall be justified ^[A1] *Text deleted* ^[A1].

NOTE The use of non-human primates for *in vivo* blood compatibility and medical device testing is prohibited by EU law (86/609/EEC) and some national laws.

6.1.12 ^[A1] The use of antithrombotics in *in vivo* and *ex vivo* tests should be avoided unless the device is designed to perform in their presence. Even if the device is designed to perform in their presence, the completion of studies without antithrombotics can also be required in order to properly assess the thrombosis risk to patients that cannot receive antithrombotics. The type and concentration of antithrombotic(s) used influence(s) blood/device interactions and their selection shall be justified. Devices that are used with antithrombotics should be assessed using them in the range of concentrations specified clinically and/or described in the product IFU or other appropriate literature. Species differences should also be considered when determining the appropriate level of antithrombotic(s).

NOTE Antithrombotics can consist of any combination of either antiplatelet drugs (e.g. acetylsalicylic acid, clopidogrel and glycoprotein IIb/IIIa receptor antagonists) or anticoagulants (e.g. unfractionated or low molecular weight heparin, warfarin and direct thrombin inhibitors), or both. ^[A1]

6.1.13 Modifications in a clinically accepted device shall be considered for their effect on blood/device interactions and clinical functions. Examples of such modifications include changes in design, geometry, changes in surface or bulk chemical composition of materials and changes in texture, porosity or other properties. An *in vitro* flow model with application-consistent exposure conditions and relevant measurements can be used to evaluate the effect of modifications to a clinically accepted device.