INTERNATIONAL STANDARD

ISO 10993-4

Second edition
2002-10-15

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
ISO 10993-4:2002(E)

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Printed in Switzerland

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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.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 3.

The main task of technical committees is to prepare International Standards. 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.

Attention is drawn to the possibility that some of the elements of this part of ISO 10993 may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

ISO 10993-4 was prepared by Technical Committee ISO/TC 194, *Biological evaluation of medical devices*.

This second edition cancels and replaces the first edition (ISO 10993-4:1992), which has been technically revised.

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

— *Part 1: Evaluation and testing*

— *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 8: Selection and qualification of reference materials for biological tests*

— *Part 9: Framework for identification and quantification of potential degradation products*

— *Part 10: Tests for irritation and sensitization*

— *Part 11: Tests for systemic toxicity*

— *Part 12: Sample preparation and reference materials*

— *Part 13: Identification and quantification of degradation products from polymeric medical devices*

— *Part 14: Identification and quantification of degradation products from ceramics*

— *Part 15: Identification and quantification of degradation products from metals and alloys*

— *Part 16: Toxicokinetic study design for degradation products and leachables*

— *Part 17: Establishment of allowable limits for leachable substances*

— *Part 18: Chemical characterization of materials*

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 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 [29]; chapters 9 and 10. This publication has since been revised [32].

Biological evaluation of medical devices —

Part 4: Selection of tests for interactions with blood

1 Scope

This part of ISO 10993 provides general requirements 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 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 normative documents contain provisions which, through reference in this text, constitute provisions of this part of ISO 10993. For dated references, subsequent amendments to, or revisions of, any of these publications do not apply. However, parties to agreements based on this part of ISO 10993 are encouraged to investigate the possibility of applying the most recent editions of the normative documents indicated below. For undated references, the latest edition of the normative document referred to applies. Members of ISO and IEC maintain registers of currently valid International Standards.

ISO 10993-1:1997, *Biological evaluation of medical devices — Part 1: Evaluation and testing*

ISO 10993-2:1992, *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 and the following 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

NOTE Such effects may or may not have clinically significant or undesirable consequences. Annex A contains further information on these interactions.

3.2
ex vivo
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 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).

3.3
thrombosis
in vivo phenomenon resulting in the partial or complete occlusion of a vessel or device by a thrombus

NOTE 1 Characterization of thrombosis includes *ex vivo* and *in vivo* methods, in either animals or the clinical setting.

NOTE 2 A thrombus is composed of a mixture of red cells, aggregated platelets, fibrin and other cellular elements.

3.4
coagulation
phenomenon that results from activation of the clotting factor cascade

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

3.5
platelet
anuclear, cellular body that is present in the circulation which adheres to surfaces and aggregates to form a hemostatic plug to minimize bleeding

NOTE Platelet testing includes quantification of platelet numbers as well as analysis of their structure and function. The testing can include analysis of platelet factors, or components on the platelet surface which are released from platelets or adherent to the device surface.

3.6
haematology
study of blood, including quantification of cellular and plasma components of the blood

3.7
complement system
part of the innate immune system, consisting of several plasma proteins, including enzymes and cellular receptors

NOTE Effector molecules produced from complement components are involved in inflammation, phagocytosis and cell lysis.

4 Abbreviated terms

Bb	product of alternative pathway complement activation
β-TG	beta-thromboglobulin
C4d	product of classical pathway complement activation
C3a, C5a	(active) complement split products from C3 and C5
CD62L	L-selectin
CH-50	50% total haemolytic complement
CT	computerized tomography
D-Dimer	specific fibrin degradation products (F XIII cross-linked fibrin)
ECMO	extracorporeal membrane oxygenator

ELISA	enzyme/linked immunosorbent assay
EM	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
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
PRP	platelet-rich plasma
PT	prothrombin time
PTT	partial thromboplastin time
P-selectin	receptor exposed during either platelet or endothelial cell release reaction
RIA	radioimmunoassay
S-12	monoclonal antibody, which recognizes the alpha-granule membrane component P-selectin 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 Types of device in contact with blood (as categorized in ISO 10993-1)

5.1 Non-contact devices

An *in vitro* diagnostic device is an example of a non-contact device.

5.2 External communicating devices

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 ISO 10993-1.

a) External communicating devices that serve as an indirect blood path include but are not limited to

- cannulae,
- extension sets,
- blood collection devices,
- devices for the storage and administration of blood and blood products (e.g. tubing, needles and bags),
- cell savers.

b) External communicating devices in contact with circulating blood include but are not limited to

- atherectomy devices,
- blood monitors,
- catheters,
- guidewires,
- intravascular endoscopes,
- intravascular ultrasound,
- intravascular laser systems,
- retrograde coronary perfusion catheters,
- cardiopulmonary bypass circuitry,
- extracorporeal membrane oxygenators,
- haemodialysis/haemofiltration equipment,
- donor and therapeutic apheresis equipment,
- devices for absorption of specific substances from blood,
- interventional cardiology and vascular devices,
- percutaneous circulatory support systems.

5.3 Implant devices

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

- annuloplasty rings,
- 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,
- embolization devices,
- endovascular grafts,
- implantable defibrillators and cardioverters,
- stents,
- arteriovenous shunts,
- blood monitors,

— internal drug delivery catheters,

— pacemaker leads,

— intravascular membrane oxygenators (artificial lungs),

— leukocyte-removal filters.

6 Characterization of blood interactions

6.1 General requirements

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 classified into five categories based on the primary process or system being measured.

Tables 1 and 2 list examples of devices which contact circulating blood and the categories of testing appropriate to the device.

NOTE Since this is a horizontal International Standard, good rationales can be developed to justify the choice of category based on the device being characterized. Thrombosis testing is frequently the preferred method for device characterization. In many cases, rationales can be used to substitute some combination of coagulation, platelets, haematology and complement system testing for thrombosis testing.

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 part of ISO 10993.

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, including duration of contact, temperature, sterile condition and flow conditions. For devices of defined geometry, the ratio of test parameter (concentration per unit volume) to exposed surface area (cm^2) shall be evaluated.

Only blood-contacting parts should be tested. The selected test methods and parameters should be in accordance with the current state of the art.

6.1.3 Controls shall be used unless their omission can be justified. Where possible, testing should include a relevant device already in clinical use or a well-characterized reference material [7].

Reference materials used should include negative and positive controls. All materials and devices 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 device or device component be tested under conditions which simulate or exaggerate clinical application.

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. For example, some short-term *in vitro* or *ex vivo* tests are poor predictors of long-term *in vivo* blood/device interactions [25], [26].

6.1.6 It follows from the above that 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.

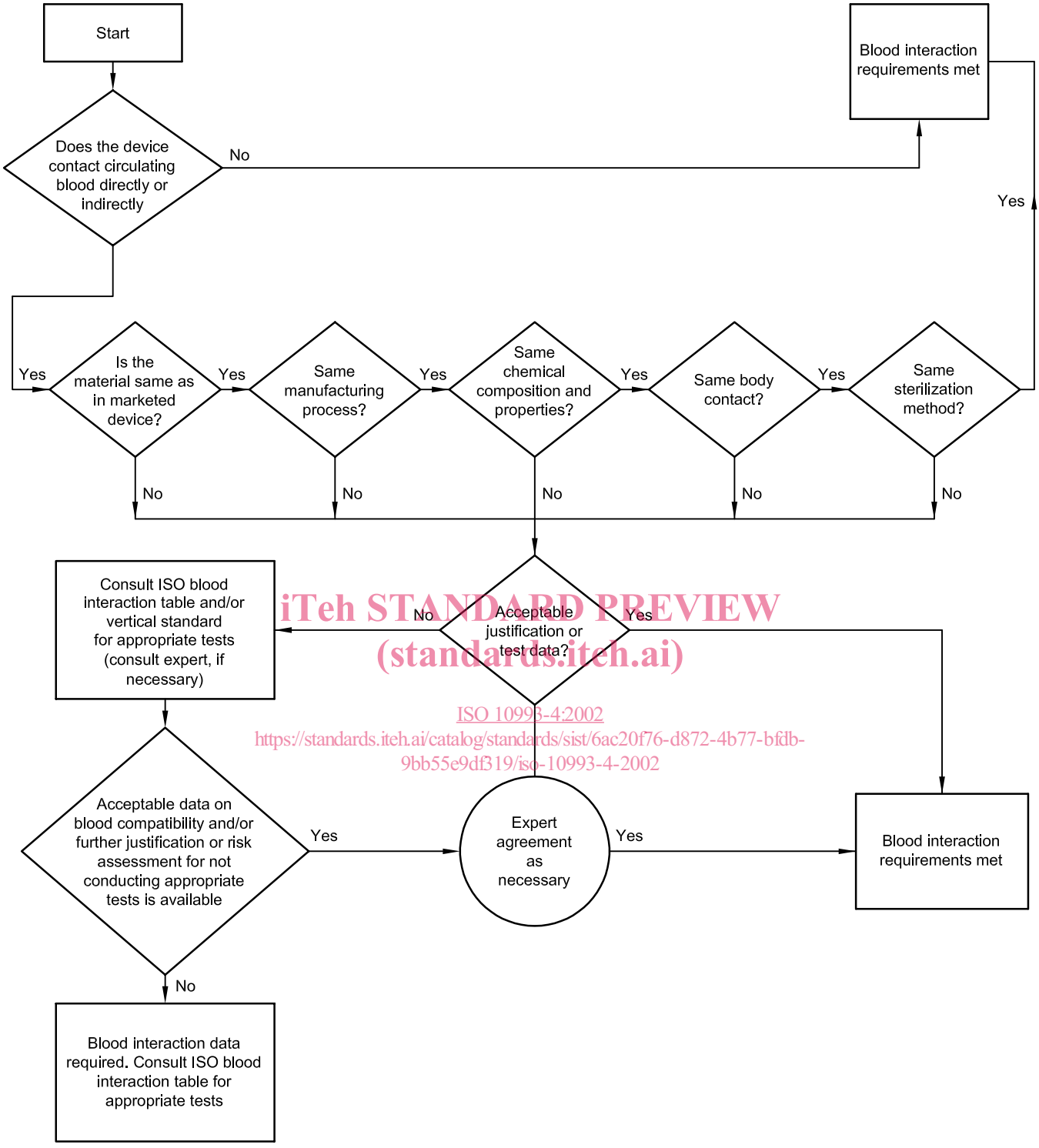

Figure 1 — Decision tree to determine whether testing for interaction with blood is necessary

Table 1 — Devices or device components which contact circulating blood and the categories of appropriate testing — External communicating devices

Device examples	Test category				
	Thrombosis	Coagulation	Platelets	Haematology	Complement system
Atherectomy devices				x[a]	
Blood monitors	x			x[a]	
Blood storage and administration equipment, blood collection devices, extension sets		x	x	x[a]	
Extracorporeal membrane oxygenator systems, haemodialysis/haemofiltration equipment, percutaneous circulatory support devices	x	x	x	x	x
Catheters, guidewires, intravascular endoscopes, intravascular ultrasound, laser systems, retrograde coronary perfusion catheters,	x	x		x[a]	
Cell savers		x	x	x[a]	
Devices for absorption of specific substances from blood		x	x	x	x
Donor and therapeutic apheresis equipment		x	x	x	x

[a] Haemolysis testing only.

Table 2 — Devices or device components which contact circulating blood and the categories of appropriate testing — Implant devices

Device examples	Test category				
	Thrombosis	Coagulation	Platelets	Haematology	Complement system
Annuloplasty rings, mechanical heart valves	x			x[a]	
Intra-aortic balloon pumps	x	x	x	x	x
Total artificial hearts, ventricular-assist devices	x			x	
Embolization devices				x[a]	
Endovascular grafts	x			x[a]	
Implantable defibrillators and cardioverters	x			x[a]	
Pacemaker leads	x			x[a]	
Leukocyte removal filter		x	x	x[a]	
Prosthetic (synthetic) vascular grafts and patches, including arteriovenous shunts	x			x[a]	
Stents	x			x[a]	
Tissue heart valves	x			x[a]	
Tissue vascular grafts and patches, including arteriovenous shunts	x			x[a]	
Vena cava filters	x			x[a]	

[a] Haemolysis testing only.