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AMENDMENT 1
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Biological evaluation of medical devices —

Part 4: Selection of tests for interactions with blood

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Évaluation biologique des dispositifs médicaux —

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

AMENDEMENT 1

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Foreword

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Amendment 1 to ISO 10993-4:2002 was prepared by Technical Committee ISO/TC 194, *Biological evaluation of medical devices*.

Biological evaluation of medical devices —

Part 4:
Selection of tests for interactions with blood

AMENDMENT 1

Page 1, Clause 1

Replace the last paragraph by the following:

"Detailed requirements for testing cannot be specified because of the limitations in knowledge and precision of tests for interactions of devices with blood. Further, 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. The selection and design of test methods 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."

Pages 2 and 3, Clause 3

Replace the whole clause by the following:

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 comprises informative text that contains further information on these interactions.

3.2
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*.

3.3
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.

3.4
embolization
process whereby a blood clot, or foreign object, is carried in the bloodstream and which may become lodged and cause obstruction downstream

3.5
***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 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.

3.6
haematology
study of blood that includes quantification of cellular and plasma components of the blood

3.7
platelets
anuclear, cellular body that is present in the circulation and which adheres to surfaces and aggregates to form a haemostatic 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 are adherent to the device surface.

3.8
thrombosis
in-vivo or *ex-vivo* phenomenon occurring in flowing whole blood involving activation of the coagulation system and platelets, which results in thrombus formation

3.9
thrombus
coagulated mixture of red cells, aggregated platelets, fibrin and other cellular elements

3.10
thromboembolization
dislodged thrombus which flows downstream and may cause subsequent vascular blockage or occlusion

Page 7, Tables 1 and 2

Replace the tables by the following:

Table 1 — Circulating blood contacting devices or device components and the categories of appropriate testing – External communicating devices

Device examples	Test category				
	Thrombosis	Coagulation	Platelets	Haematology	Complement system
Catheters in place for less than 24 h (e.g. atherectomy devices, guide wires)	×[a]			×[b]	
Blood monitors	×[a]			×[b]	
Blood storage and administration equipment, blood collection devices, extension sets		×	×	×[b]	×[c]
Catheters in place for more than 24 h (e.g., intravascular endoscopes, intravascular ultrasound, lasers systems, retrograde coronary perfusion catheters)	×[a]			×[b]	×
Cell savers		×	×	×[b]	
Devices for absorption of specific substances from blood		×	×	×	×
Donor and therapeutic aphaeresis equipment and cell separation systems		×	×	×	×
Extracorporeal membrane oxygenators system Haemodialysis/haemofiltration equipment Percutaneous circulatory support devices	×[a]			×	×
Leukocyte removal filter		×	×	×[b]	×

[a] As stated in 3.8, thrombosis is an *in-vivo* or *ex-vivo* phenomenon. It is recognized that coagulation and platelet responses are involved in this process. Therefore, it is up to the manufacturer, to decide if specific testing in the coagulation and platelet test categories are appropriate for their device.

[b] Haemolysis testing only.

[c] Only for aphaeresis equipment and related procedures.

Table 2 — Circulating blood contacting devices or device components and the categories of appropriate testing – Implant devices

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

[a] As stated in 3.8, thrombosis is an *in-vivo* or *ex-vivo* phenomenon. It is recognized that coagulation and platelet responses are involved in this process. Therefore, it is up to the manufacturer to decide if specific testing in the coagulation and platelet test categories are appropriate for their device.

[b] Haemolysis testing only.

Page 8, subclause 6.1.7

Delete the whole clause and renumber the 6.1.8 to 6.1.14 as 6.1.7 to 6.1.13.

New subclause 6.1.7

Replace the whole clause by the following:

"The recommendations in 6.1.5 and 6.1.6, together with Clause 5, Figure 1 and Table 2 serve as a guide for the selection of tests listed in 6.2.1. Guidance on pre-clinical evaluations is given in Annex A. The following procedure shall be performed:

a) determine which of the 5 potential blood interaction categories are appropriate to the device;

b) evaluate existing information on reactions within these categories;

c) select appropriate tests from Table 3 or 4."