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AMENDMENT 1
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Biological evaluation of medical devices —

Part 4: Selection of tests for interactions with blood

AMENDMENT 1

Évaluation biologique des dispositifs médicaux —
Partie 4: Choix des essais pour les interactions avec le sang
AMENDEMENT 1

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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, *Biological and clinical evaluation of medical devices,* in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

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3.4

Replace "ISO/TR 10993-20" with "ISO/TS 10993-20" in Note 1 to entry.

5.2.2

Replace the subclause heading with:

Biological evaluation of medical devices —

Part 4:
Selection of tests for interactions with blood

AMENDMENT 1

5.2.2 External communicating devices indirectly contacting blood

Delete the bullet points “cannulae”, “cell savers”, “intravascular catheters” and “blood collection devices”.

Replace “blood and blood product” with “saline and/or therapeutics” as follows:

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

Add the bullet point “blood monitors with indirect blood contact” as the second bullet point.

5.2.3

Add “blood collection devices” as a second bullet point, “cannulae” as a fourth bullet point, “cell savers” as a sixth bullet point and “devices for the storage and administration of blood and blood products (e.g. tubing and bags)” as an eighth bullet point.

Delete “or indirect” in the third bullet point as follows:

— blood monitoring devices with direct blood contact;

6.1.2

Add the following text to the second paragraph after the sentence “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 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.

Replace the fourth paragraph with:

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.

6.1.4

Replace NOTE 1 with:

NOTE 1 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.

6.1.6

Replace Table 1 with:

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

Device examples	Test category						
	Haemolysis		Thrombosis[c]				
			In vitro				In vivo or ex vivo[a]
	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.

Table 1 *(continued)*

Device examples	Test category								
	Haemolysis		Thrombosis[c] In vitro						In vivo or ex vivo[a]
	Material-induced	Mechanically-induced	Coagulation	Platelet activation	Complement[d]	Haematology			
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, 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 endpoints 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.

6.1.11

Delete “(see also ISO 10993-2)” at the end of the second paragraph.

6.1.12

Replace the paragraph with:

> 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).

Add the following NOTE at the end of this paragraph:

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.

6.1.14

Delete "see ISO 10993-2" and add the following NOTE after the paragraph:

NOTE For more information on animal welfare, see ISO 10993-2.

6.3.1

Replace “Alternatives to the latter may be feasible if validated.” with:

> The use of blood older than 4 h may be feasible for certain tests, if validated alongside freshly obtained blood or by other scientifically sound methods.

A.1.1

Delete “of non-contact-, externally communicating and implant devices” from the sentence as follows: “and a list of tests for evaluating blood/device interactions.”

A.1.4

Replace the first sentence of the third paragraph with:

> The classical Chandler loop in vitro test model[43] or modifications thereof[193][194][195][199][200][203] are examples of models used to test for general material or device haemocompatibility under physiological and/or quasi-physiological flow conditions.