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Cardiovascular implants and extracorporeal systems — Blood/tissue contact surface modifications for extracorporeal perfusion systems

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National foreword

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The UK participation in its preparation was entrusted to Technical Committee CH/150/2, Cardiovascular implants.

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

This publication does not purport to include all the necessary provisions of a contract. Users are responsible for its correct application.

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Implants cardiovasculaires et systèmes extracorporels — Revêtements pour l'équipement au contact du sang

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Foreword

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International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

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 document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

ISO 11658 was prepared by Technical Committee ISO/TC 150, *Implants for surgery*, Subcommittee SC 2, *Cardiovascular implants and extracorporeal systems*.

Introduction

This International Standard is intended to ensure that devices that have surface modified blood-contacting surfaces are tested for their safety, integrity and function, and that extracorporeal device characteristics are appropriately disclosed when labelling the device. This International Standard also includes minimum reporting requirements, which will allow the user to compare properties in a standard way.

This International Standard therefore contains recommended procedures to be used for evaluation of modified surfaces. The requirements for determination of the surface coverage, leaching and biological activity, if claimed, of the surface modification are addressed, although limits for these requirements are not specified.

This International Standard makes reference to other International Standards in which methods for determination of characteristics common to medical devices can be found.

Requirements for animal and clinical studies have not been included in this International Standard.

Additional requirements are covered by references to other International Standards listed in the normative references.

INTERNATIONAL STANDARD ISO 11658:2012(E)

Cardiovascular implants and extracorporeal systems — Blood/tissue contact surface modifications for extracorporeal perfusion systems

1 Scope

This International Standard specifies requirements for the physical, biological and performance testing of biocompatible modifications on extracorporeal devices. This International Standard is applicable to components of heart-lung bypass equipment and of extracorporeal life support equipment that carry blood and have modifications on the blood and tissue-contacting surfaces of the device.

The assumption is that these devices will be used at conventional ranges of hypothermia and normothermia. If hyperthermia (>37 °C) applications are indicated, then testing is performed over the indicated range.

2 Normative references

The following referenced documents are indispensable for the application 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 7199, *Cardiovascular implants and artificial organs — Blood-gas exchangers (oxygenators)*

ISO 10993-1, *Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process*

ISO 10993-7, *Biological evaluation of medical devices — Part 7: Ethylene oxide sterilization residuals*

ISO 10993-11, *Biological evaluation of medical devices — Part 11: Tests for systemic toxicity*

ISO 11135-1, *Sterilization of health care products — Ethylene oxide — Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices*

ISO 11137-1, *Sterilization of health care products — Radiation — Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices*

ISO 14937, *Sterilization of health care products — General requirements for characterization of a sterilizing agent and the development, validation and routine control of a sterilization process for medical devices*

ISO 15674, *Cardiovascular implants and artificial organs — Hard-shell cardiotomy/venous reservoir systems (with/without filter) and soft venous reservoir bags*

ISO 15675, *Cardiovascular implants and artificial organs — Cardiopulmonary bypass systems — Arterial blood line filters*

ISO 15676, *Cardiovascular implants and artificial organs — Requirements for single-use tubing packs for cardiopulmonary bypass and extracorporeal membrane oxygenation (ECMO)*

ISO 17665-1, *Sterilization of health care products — Moist heat — Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices*

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

3.1
surface modification
modification that can be biologically derived or non-biologically derived and can be applied to blood-contacting surfaces or additives incorporated into a material as part of the manufacturing process

3.2
coverage
extent to which a surface modification applied to a blood contact device effectively covers the blood or tissue-contacting surface of the device

3.3
leaching
extent to which a surface modification applied to the surface of a blood contact device may elute from the surface of the device directly contacting the patient or into the fluid stream which in turn contacts the patient

3.4
bioactivity
quantification of any biological activity that a surface modification applied to the surface of a blood contact device imparts to the blood or tissues to which it is exposed

4 Requirements

4.1 Biological characteristics

4.1.1 Sterility and non-pyrogenicity

The blood pathway shall be sterile and non-pyrogenic. Compliance shall be verified in accordance with 5.2.1.

4.1.2 Biocompatibility

Parts of the blood pathway shall be biocompatible with respect to their intended use. Compliance shall be verified in accordance with 5.2.2.

4.1.3 Biological activity

If any claims of biological activity are made by the manufacturer, then quantification of such claims shall be verified by the manufacturer in accordance with 5.2.3.

4.2 Physical characteristics

4.2.1 Blood pathway integrity

When tested in accordance with 5.3.1, the blood pathway shall not leak.

4.2.2 Blood pathway coverage

The surfaces which are covered by the surface modification shall be verified by the manufacturer in accordance with 5.3.2.

4.2.3 Surface modification integrity

The integrity of the surface modification shall be verified by the manufacturer in accordance with 5.3.3.

4.3 Performance characteristics

4.3.1 Blood cell damage

When determined in accordance with 5.4.1, the percentage change (positive or negative) of plasma-free haemoglobin, platelets and white blood cells shall be within the range of values specified by the manufacturer.

4.3.2 General performance

When determined in accordance with 5.4.2, the ability of the device to perform its intended function with the biocompatible surface modification in place shall be verified by the manufacturer.

4.3.3 Shelf life

When tested in accordance with 5.4.3, test results shall demonstrate the rated shelf life.

5 Tests

5.1 General

5.1.1 Tests and measurements shall be performed with the device in its terminally sterilized form, and prepared according to the manufacturer's instructions for intended clinical use.

5.1.2 Operating variables shall be those specified by the manufacturer for intended clinical use, unless otherwise specified.

5.1.3 The temperature of the test liquid(s) shall be representative of a range of the intended clinical temperatures during device use (e.g. hypothermic, normothermic and/or hyperthermic). Tests should be performed at multiple temperatures over the range of the intended clinical use, or justification for testing at a single temperature should be provided (e.g. why this temperature is representative of the worst-case condition).

5.1.4 If the relationship between variables is non-linear, sufficient determinations shall be made to permit valid interpolation between data points.

5.1.5 The test or measurement procedures are to be regarded as reference procedures. Other procedures can be accepted, provided that the alternative procedure has been shown to be of comparable precision and reproducibility.

5.2 Biological characteristics

5.2.1 Sterility and non-pyrogenicity

Compliance shall be verified by inspection of the manufacturer's documentation on sterilization and pyrogen testing, in accordance with ISO 17665-1, ISO 11135-1, ISO 11137-1, ISO 14937 or ISO 10993-11, as applicable.

5.2.2 Biocompatibility

Compliance shall be verified by test or by inspection of the manufacturer's documentation on biocompatibility for the finished device, in accordance with ISO 10993-1 and ISO 10993-7, as applicable.

5.2.3 Biological activity

Any biological activity claims shall be verified using validated methodology performed according to the manufacturer's protocol. This shall not apply to surface modifications for which biological activity is not claimed.

EXAMPLE A claim of heparin activity can be verified with a test to evaluate the anticoagulant activity in terms of antithrombin uptake and the concomitant thrombin inhibitory capacity of the heparin present in the surface modification.

5.3 Physical characteristics

5.3.1 Determination of blood pathway integrity (sterile final assembly)

Devices that have established standards, such as oxygenators, reservoirs, tubing packs and arterial filters, shall use the prescribed methodology from their respective standard for testing.

In the absence of an established standard, subject the blood pathway of the device, filled with water, to a negative or positive pressure of 1,5 times the manufacturer's rated pressure, or, if none is given, to a pressure of 152 kPa (22 psi) gauge. Maintain this pressure for 6 h or for the intended use time specified by the manufacturer. Visually inspect the device for evidence of water leakage.

5.3.2 Determination of surface modification coverage

Any surface modification coverage claims shall be verified using validated methodology performed according to the manufacturer's protocol.

EXAMPLE A claim of coverage for a heparin-containing surface modification can be verified by treating coated devices with the cationic dye, toluidine blue. The dye is absorbed onto the negatively charged surface inducing a metachromatic shift in the colour of the dye (blue to purple). The coverage of the stained surface is then visually inspected for purple colour distribution.

5.3.3 Determination of surface modification integrity

The integrity of the surface modification shall be verified using validated methodology performed according to the manufacturer's protocol.

Such testing shall be performed using an appropriate extraction media under conditions simulating the maximum rated conditions as specified for the device. These conditions shall include the temperature, flow rate, pressure, duration of testing (6 h or intended duration of use), and mechanical stress (such as roller pump compression of tubing indicated for use in a roller pump) for the intended purpose of the device specified by the manufacturer.

5.4 Performance characteristics

5.4.1 Blood cell damage

Devices that have established standards, such as oxygenators, reservoirs, tubing packs and arterial filters, shall use the prescribed methodology from their respective standard for testing.

In the absence of an established standard, the manufacturer shall assess the blood cell trauma of the device according to the manufacturer's internal procedures.

5.4.2 General performance

Device performance that is expected to be affected by the surface modification shall be tested.

Devices that have established standards, such as oxygenators, reservoirs, tubing packs and arterial filters, shall use the prescribed methodology from their standard for testing.

In the absence of an established standard, the manufacturer shall assess the performance characteristics of the device as per the manufacturer's internal procedures.

5.4.3 Shelf life

Using a documented method, the finished, packaged devices shall be artificially aged to determine nominal shelf life. A real-time or accelerated aging process shall be performed on finished devices to confirm statistically relevant mean shelf life.

6 Information supplied by the manufacturer

6.1 General

Manufacturers shall provide the information specified in the following ISO device standards:

— for oxygenators, ISO 7199;

— for reservoirs, ISO 15674;

— for arterial filters, ISO 15675;

— for tubing packs, ISO 15676.

For devices with a surface modification, the additional information specified in 6.2 shall be provided.

6.2 Information to be given in the accompanying documents

Each shipping container shall contain an “Instructions for Use” leaflet with the following information.

a) Coverage: a statement indicating the extent to which the modification effectively covers the blood- or tissue-contacting surface of the device. If such a modification is not present on all blood- or tissue-contacting surfaces of the device, a clear description shall be provided of what components are and are not modified.

b) Leaching: if changes in the modification during use or elution of the modification have adverse clinical effects, they should be described.

c) Bioactivity (if there is a claim of bioactivity for the modification): a statement quantifying the manufacturer’s specification for any biological activity that the modification will impart to the blood or tissues to which it is exposed.

d) A statement that the test methods used to determine coverage, leaching and bioactivity (if applicable) are available upon request.

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