BS EN ISO 8637:2014

BSI Standards Publication

Cardiovascular implants and extracorporeal systems — Haemodialysers, haemodiafilters, haemofilters and haemoconcentrators (ISO 8637:2010, including Amendment 1 2013-04-01)

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National foreword

This British Standard is the UK implementation of EN ISO 8637:2014. It is identical to ISO 8637:2010, incorporating amendment 1:2013. Together with BS EN ISO 8368:2014, it supersedes BS EN 1283:1996, which is withdrawn.

ISO amendment 1:2013 updates Figure 2.

The UK participation in its preparation was entrusted by Technical Committee CH/150, Implants for surgery, to Subcommittee CH/150/2, Cardiovascular implants.

A list of organizations represented on this subcommittee 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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Date	Text affected

EUROPEAN STANDARD

NORME EUROPÉENNE

EUROPÄISCHE NORM

EN ISO 8637

January 2014

ICS 11.040.40

English Version

Cardiovascular implants and extracorporeal systems - Haemodialysers, haemodiafilters, haemofilters and haemoconcentrators (ISO 8637:2010, including Amendment 1 2013-04-01)

Implants cardiovasculaires et systèmes extracorporels - Hémodialyseurs, hémodiafiltres, hémofiltres et hémoconcentrateurs (ISO 8637:2010, Amendement 1 2013-04-01 inclus)

Kardiovaskuläre Implantate und extrakorporale Systeme - Hämodialysatoren, Hämodiafilter, Hämofilter und Hämokonzentratoren (ISO 8637:2010, einschließlich Änderung 1 2013-04-01)

This European Standard was approved by CEN on 1 December 2013.

CEN members are bound to comply with the CEN/CENELEC Internal Regulations which stipulate the conditions for giving this European Standard the status of a national standard without any alteration. Up-to-date lists and bibliographical references concerning such national standards may be obtained on application to the CEN-CENELEC Management Centre or to any CEN member.

This European Standard exists in three official versions (English, French, German). A version in any other language made by translation under the responsibility of a CEN member into its own language and notified to the CEN-CENELEC Management Centre has the same status as the official versions.

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EUROPEAN COMMITTEE FOR STANDARDIZATION
COMITÉ EUROPÉEN DE NORMALISATION
EUROPÄISCHES KOMITEE FÜR NORMUNG

CEN-CENELEC Management Centre: Avenue Marnix 17, B-1000 Brussels

Foreword

The text of ISO 8637:2010, including Amendment 1 2013-04-01 has been prepared by Technical Committee ISO/TC 150 “Implants for surgery” of the International Organisation for Standardization (ISO) and has been taken over as EN ISO 8637:2014 by Technical Committee CEN/TC 205 “Non-active 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 July 2014, and conflicting national standards shall be withdrawn at the latest by July 2014.

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

This document supersedes EN 1283:1996.

According to the CEN-CENELEC Internal Regulations, the national standards organizations of the following countries are bound to implement this European Standard: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, Former Yugoslav Republic of Macedonia, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey and the United Kingdom.

Endorsement notice

The text of ISO 8637:2010 has been approved by CEN as EN ISO 8637:2014 without any modification.

Annex ZA
(informative)
Relationship between this European Standard and the Essential Requirements of EU Directive 93/42/EEC on medical devices

This European Standard has been prepared under a mandate given to CEN by the European Commission and the European Free Trade Association to provide a means of conforming to Essential Requirements of the New Approach Directive 93/42/EEC on medical devices.

Once this standard is cited in the Official Journal of the European Union under that Directive and has been implemented as a national standard in at least one Member State, compliance with the clauses of this standard given in Table ZA.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.

Table ZA.1 — Correspondence between this European Standard and Directive 93/42/EEC on medical devices *(1 of 2)*

Clause(s)/sub-clause(s) of this EN	Essential Requirements (ERs) of Directive 93/42/EEC	Qualifying remarks/Notes
4.1, 4.2, 4.3	7.2	
4.1	7.3	
4.1	7.4	Addressed only in general terms. Blood-contacting surfaces incorporating medicinal products, such as heparin, are not specifically addressed.
4.1, 6.4(n)	7.5	Addressed only in general terms. Typically, these devices do not incorporate materials containing phthalates.
4.2, 4.3, 6.1(h), 6.1(i), 6.2(e), 6.2(f), 6.2(h), 6.3(f), 6.3(g), 6.4(c), 6.4(f), 6.4(g), 6.4(i)	8.1	
4.2, 5.3	8.3	Addressed only in general terms.
4.2, 5.3	8.4	
4.4.3, 4.4.4, 4.4.5, 4.4.6	9.1	Connectors are specified to match tubing connectors specified in ISO 8638 for the blood compartment.
4.4.4	12.7.4	
6	13.1	
6.1, 6.2, 6.3, 6.4	13.2	The NOTE at the end of each clause allows the use of symbols from Harmonized Standards.

Table ZA.1 ***(2 of 2)***

Clause(s)/sub-clause(s) of this EN	**Essential Requirements (ERs) of Directive 93/42/EEC**	**Qualifying remarks/Notes**
6.1(a), 6.2(a), 6.3(a), 6.3(b), 6.4(a)	13.3 (a)	
6.1(b), 6.1(c), 6.2(b), 6.2(c), 6.3(c), 6.3(d), 6.4(b), 6.4(e)	13.3 (b)	
6.2(e), 6.3(f), 6.4(f)	13.3 (c)	
6.1(d), 6.2(d), 6.3(e)	13.3 (d)	
6.1(g), 6.2(g), 6.3(h)	13.3 (e)	
6.1(i), 6.2(h), 6.4(g)	13.3 (f)	
6.3(g)	13.3 (i)	
6.4(c), 6.4(d), 6.4(i)	13.3 (j)	
6.2(j), 6.4(d)	13.3 (k)	
6.1(h), 6.2(f), 6.4(f)	13.3 (m)	
6.4(a), 6.4(b), 6.4(e), 6.4(f), 6.4(g), 6.4(i), 6.4(f)	13.6 (a)	There is no requirement for the information in 13.3 (i) in the instructions for use. Instead, that information is required to be given on the outer container in which the device is sold.
6.4(h)	13.6 (b)	
6.4(l), 6.4(m)	13.6 (c)	
6.2(h), 6.4(g), 6.4(i)	13.6 (h)	
6.4(c), 6.4(d)	13.6 (i)	

WARNING — Other requirements and other EU Directives may be applicable to the product(s) falling within the scope of this standard.

INTERNATIONAL STANDARD

ISO 8637

Third edition
2010-07-01

Cardiovascular implants and extracorporeal systems — Haemodialysers, haemodiafilters, haemofilters and haemoconcentrators

Implants cardiovasculaires et systèmes extracorporels — Hémodialyseurs, hémodiafiltres, hémofiltres et hémoconcentrateurs

Reference number
ISO 8637:2010(E)

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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 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 8637 was prepared by Technical Committee ISO/TC 150, *Implants for surgery*, Subcommittee SC 2, *Cardiovascular implants and extracorporeal systems*.

This third edition cancels and replaces the second edition (ISO 8637:2004), which has been technically revised.

Introduction

This International Standard is concerned with devices intended for haemodialysis, haemodiafiltration, haemofiltration and haemoconcentration in humans. The requirements specified in this International Standard will help to ensure safety and satisfactory function.

It was not found practicable to specify materials of construction. This International Standard therefore requires only that materials have been tested and that the methods and results are made available upon request. There is no intention to specify, or to set limits on, the performance characteristics of the devices because such restrictions are unnecessary for the qualified user and would limit the alternatives available when choosing a device for a specific application.

The dimensions of the blood ports and the dialysis fluid or filtrate ports have been specified to ensure compatibility of the device with the extracorporeal blood circuit specified in ISO 8638. The design and dimensions have been selected in order to minimize the risk of leakage of blood and the ingress of air.

This International Standard reflects the consensus of physicians, manufacturers and other interested parties for devices that are approved for clinical use. Conformance with this International Standard is voluntary and it does not supersede any national regulation.

Cardiovascular implants and extracorporeal systems — Haemodialysers, haemodiafilters, haemofilters and haemoconcentrators

1 Scope

This International Standard specifies requirements for haemodialysers, haemodiafilters, haemofilters and haemoconcentrators, hereinafter collectively referred to as “the device”, for use in humans.

This International Standard is not applicable to:

— extracorporeal blood circuits;

— plasmafilters;

— haemoperfusion devices;

— vascular access devices;

— blood pumps;

— pressure monitors for the extracorporeal blood circuit;

— air detection devices;

— systems to prepare, maintain or monitor dialysis fluid;

— systems used to perform haemodialysis, haemodiafiltration, haemofiltration or haemoconcentration;

— reprocessing procedures and equipment.

NOTE Requirements for the extracorporeal blood circuit for haemodialysers, haemodiafilters and haemofilters are specified in ISO 8638.

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 594-2, *Conical fittings with 6 % (Luer) taper for syringes, needles and certain other medical equipment — Part 2: Lock fittings*

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

ISO 10993-4, *Biological evaluation of medical devices — Part 4: Selection of tests for interactions with blood*

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*

3 Terms and definitions

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

3.1
blood compartment
part of a haemodialyser (3.12), haemodiafilter (3.10), haemofilter (3.14) or haemoconcentrator (3.9) through which blood is intended to pass

NOTE For hollow-fibre devices, the blood compartment includes the volume of the hollow fibres plus the headers.

3.2
clearance
volume of a solution from which a solute is completely removed per unit time

3.3
convection
transport of solutes across a semipermeable membrane, along with filtered fluid, caused by a pressure gradient or pressure differential across the membrane

3.4
dialysis fluid
aqueous fluid containing electrolytes and, usually, buffer and glucose, which is intended to exchange solutes with blood during haemodialysis (3.13) or haemodiafiltration (3.11)

NOTE 1 The term “dialysis fluid” is used throughout this International Standard to mean the fluid (made from dialysis water and concentrates) which is delivered to the haemodialyser or haemodiafilter by the dialysis fluid delivery system. Such phrases as “dialysate”, “dialysis solution” or “dialysing fluid” can be used in place of dialysis fluid.

NOTE 2 The dialysis fluid entering the haemodialyser or haemodiafilter is referred to as “fresh dialysis fluid”, while the fluid leaving the haemodialyser or haemodiafilter is referred to as “spent dialysis fluid”.

NOTE 3 Dialysis fluid does not include pre-packaged parenteral fluids used in some renal replacement therapies, such as haemodiafiltration and haemofiltration.

3.5
dialysis fluid compartment
part of a haemodialyser (3.12) or haemodiafilter (3.10) through which dialysis fluid (3.4) is intended to pass

3.6
diffusion
transport of solutes across a semipermeable membrane, caused by a concentration gradient

3.7
filtrate
fluid removed from the blood across the semipermeable membrane into the dialysis fluid or filtrate compartment of a haemodialyser (3.12), haemodiafilter (3.10), haemofilter (3.14) or haemoconcentrator (3.9), due to a pressure gradient (including the contributions of both hydrostatic and oncotic pressures) across the semipermeable membrane

3.8
haemoconcentration
process whereby plasma water and electrolytes are removed from diluted blood across a semipermeable membrane

3.9
haemoconcentrator
device intended to perform haemoconcentration (3.8)

3.10
haemodiafilter
device intended to perform haemodiafiltration (3.11)

3.11
haemodiafiltration
process whereby solute imbalances in a patient's blood are corrected by means of simultaneous convection and diffusion across a semipermeable membrane, and by replacement with an appropriate physiological fluid

NOTE Normally, the process also includes a net fluid removal.

3.12
haemodialyser
device intended to perform haemodialysis (3.13)

3.13
haemodialysis
process whereby solute imbalances in a patient's blood are corrected, mainly by diffusion across a semipermeable membrane

NOTE Normally, the process also includes a net fluid removal.

3.14
haemofilter
device intended to perform haemofiltration (3.15)

3.15
haemofiltration
process whereby solute imbalances in a patient's blood are corrected, mainly by convection across a semipermeable membrane and replacement with an appropriate physiological fluid

NOTE Normally, the process also includes a net fluid removal.

3.16
labelling
written, printed, graphic or electronic matter that:

— is affixed to a medical device or any of its containers or wrappers

or

— accompanies a medical device and which is related to identification, technical description and use of that medical device, but excluding shipping documents

3.17
sieving coefficient
ratio of a solute concentration in the filtrate to the simultaneous concentration of the same solute in the plasma

3.18
transmembrane pressure
TPM
p_{TM}
mean pressure exerted across a semipermeable membrane

NOTE For practical reasons, the mean TMP is generally expressed as either:

— the difference between arithmetic means of inlet and outlet pressures of the blood and dialysis fluid compartments of a haemodialyser or a haemodiafilter

or

— the difference between the arithmetic mean of the inlet and outlet pressures of the blood compartment and the filtrate pressure of a haemofilter or a haemoconcentrator.

3.19
ultrafiltration coefficient
permeability of membrane to water, generally expressed in millilitres per hour per millimetre of mercury

4 Requirements

4.1 Biological safety

Parts of the device that are intended to come into direct or indirect contact with blood shall be evaluated for freedom from biological hazards, in accordance with 5.2. If the device is labelled for reuse, testing shall be performed after reprocessing following the manufacturer's instructions for use.

Attention is drawn to the need to establish whether national regulations or national standards governing toxicology and biocompatibility testing exist in the country in which the device is produced and, if applicable, in the countries in which the device is to be marketed.

4.2 Sterility

The blood pathway of the device shall be sterile. Compliance shall be verified in accordance with 5.3.

4.3 Non-pyrogenicity

The blood pathway of the device shall be non-pyrogenic. Compliance shall be verified in accordance with 5.4.

4.4 Mechanical characteristics

4.4.1 Structural integrity

The device shall be capable of withstanding a positive pressure of 1,5 × the manufacturer's recommended maximum pressure and a negative pressure not exceeding 700 mmHg (93,3 kPa below atmospheric pressure) or the highest obtainable negative pressure if at high elevation, when tested according to 5.5.1.

NOTE This requirement refers to the external case integrity of the device.

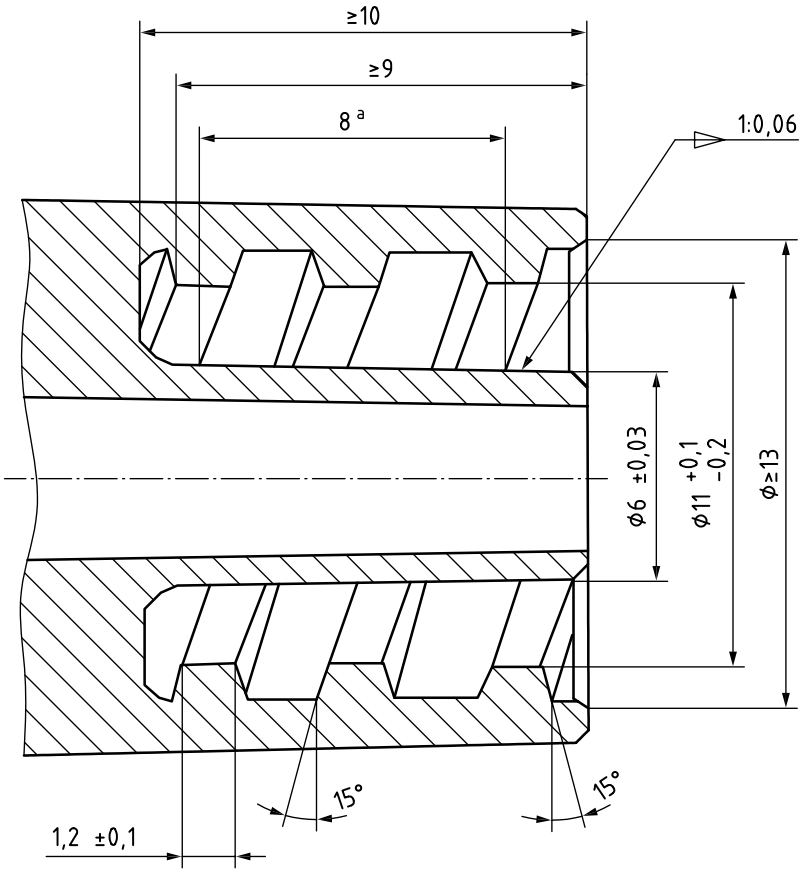
4.4.2 Blood compartment integrity

When exposing the blood compartment to a validated test procedure performed at 1,5 × the manufacturer's maximum recommended transmembrane pressure, the blood compartment shall not leak. Compliance with this requirement shall be verified in accordance with 5.5.2.

4.4.3 Haemodialyser, haemodiafilter and haemofilter blood compartment ports

Except where the haemodialyser, haemodiafilter or haemofilter and the extracorporeal blood circuit are designed as an integral system, the dimensions of the blood ports shall be as given in Figure 1. Compliance with this requirement shall be verified in accordance with 5.5.3.

Dimensions in millimetres



[a] Double thread.

Figure 1 — Main fitting dimensions of blood inlet and outlet ports

4.4.4 Haemodialyser and haemodiafilter dialysis fluid compartment ports

Except where the haemodialyser or haemodiafilter and the dialysis fluid circuit are designed as an integral system, the dimensions of the dialysis fluid compartment ports shall be as given in Figure 2. Compliance with this requirement shall be verified in accordance with 5.5.4.

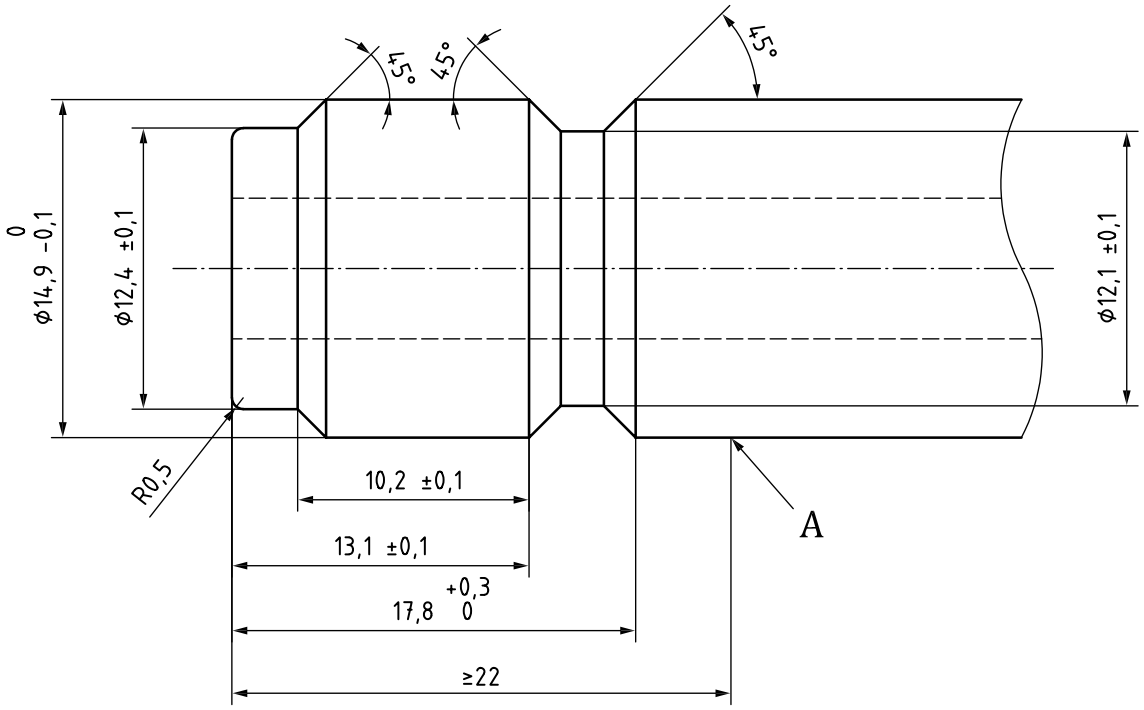
4.4.5 Haemofilter filtrate ports

Except where the haemofilter and the filtrate circuit are designed as an integral system, the filtrate ports of haemofilters shall comply either with Figure 2 or with the requirements of the Luer lock fitting of ISO 594-2. Compliance with this requirement shall be verified in accordance with 5.5.5.

4.4.6 Haemoconcentrator blood and filtrate ports

The blood and filtrate ports of haemoconcentrators shall allow for a secure connection to the tubing which is to be used with the device. Compliance with this requirement shall be verified in accordance with 5.5.6.

Dimensions in millimetres



Key

A necessary length and diameter for engagement with female connectors of dialysis fluid circuit

Figure 2 — Main fitting dimensions of dialysis fluid inlet and outlet ports

4.5 Performance characteristics

4.5.1 Clearance of haemodialysers and haemodiafilters

The clearance of urea, creatinine, phosphate and vitamin B_{12} shall be determined in accordance with 5.6.1. Blood and dialysis fluid flow rates shall cover the manufacturer's specified range.

NOTE As a supplement, K_0A results can be included.

4.5.2 Sieving coefficient of haemodiafilters, haemofilters and haemoconcentrators

The sieving coefficient for albumin, inulin and myoglobin or β_2-microglobulin shall be determined in accordance with 5.6.2.

4.5.3 Ultrafiltration coefficient

The ultrafiltration coefficient shall be determined in accordance with 5.6.3. Testing shall be conducted over the manufacturer's specified range of transmembrane pressures and blood flow rates.

4.5.4 Volume of the blood compartment

The volume of the blood compartment shall be determined in accordance with 5.6.4 over the specified range of transmembrane pressures.

NOTE If the blood compartment is noncompliant, it is acceptable to determine the volume at one transmembrane pressure.

4.5.5 Pressure drop of the blood compartment

The pressure drop of the blood compartment shall be determined in accordance with 5.6.5.

4.6 Expiry date

The biological safety, sterility and mechanical integrity of the device shall be proven after storage for a period corresponding to the expiry date. Compliance shall be in accordance with 5.7.

5 Test methods

5.1 General

The performance characteristics specified in 4.5 shall be determined prior to marketing a new type of device and shall be re-evaluated after changes in the device that might alter its performance. If labelled for multiple uses, devices shall be tested for clearances and ultrafiltration coefficient after reprocessing according to the manufacturer's instructions to characterize the effects of the recommended cleaning agent and germicide on membrane performance.

The sample of devices shall be drawn at random from the manufacturer's production and shall have passed all applicable quality control steps, as well as sterilization, if applicable. They shall be prepared according to the manufacturer's recommendations as though they are to be used for a clinical procedure.

Measurements shall be made *in vitro* at (37 ± 1) °C. When the relationship between variables is non-linear, sufficient determinations shall be made to permit interpolation between the data points. The techniques of measurement given in this International Standard are reference tests. Other test methods may be used, provided they have been validated and shown to be precise and reproducible.

The test systems shown do not indicate all the necessary details of practicable test apparatus. The design and construction of actual test systems and the establishment of actual test systems shall also address the many factors contributing to measurement error, including, but not limited to, pressure measurement errors due to static head effects and dynamic pressure drops; parameter stabilization time; uncontrolled temperature variations at the non-constant flow rates; pH; degradation of test substances due to heat, light and time; degassing of test fluids; trapped air; and system contamination by foreign material, algae and bacteria.

NOTE Clause 5 contains tests that are of a type-testing nature, such as the ones described in 5.5.1, 5.5.3, 5.5.4, 5.6.1, 5.6.2, 5.6.3 and 5.6.4, which are carried out prior to marketing of a new device or when changes are made to the device or its manufacturing processes. Others are of a quality control nature, such as the ones described in 5.3, 5.4 and 5.5.2, which are repeated on a regular basis in accordance with quality management system requirements.

5.2 Biological safety

The biological safety of haemodialysers, haemodiafilters, haemofilters and haemoconcentrators that are intended to come into direct or indirect contact with the patient's blood shall be evaluated on samples of each new type of device prior to its marketing, or after any change in the materials of construction of that type of device, or after any change in the method of sterilization. If labelled for multiple use, testing shall demonstrate the safety of the device before first use and after reprocessing according to the manufacturer's instructions. Testing shall be carried out in accordance with ISO 10993-1, ISO 10993-4, ISO 10993-7 or ISO 10993-11, as relevant.

5.3 Sterility

Compliance with 4.2 shall be verified by inspection of the records to show that the device has been exposed to a validated sterilization process.

5.4 Non-pyrogenicity

Compliance with 4.3 shall be verified in accordance with ISO 10993-11.

5.5 Mechanical characteristics

5.5.1 Structural integrity

5.5.1.1 General

The requirements of 4.4.1 shall be verified by the following test methods.

5.5.1.2 Positive-pressure test

Completely fill the device with degassed water at (37 ± 1) °C. Seal all ports except the port to which pressure is applied. Apply a positive pressure 1,5 × the manufacturer's recommended maximum pressure and seal the apparatus. After 10 min, record the pressure and visually examine the device for leaks.

5.5.1.3 Negative pressure test

Completely fill the device with degassed water at (37 ± 1) °C. Seal all ports except the port to which pressure is applied. Put the device under sub-atmospheric pressure, 1,5 × the manufacturer's recommended maximum pressure, unless that sub-atmospheric pressure exceeds 700 mmHg or is not specified; in that case, apply a sub-atmospheric pressure of 700 mmHg (93,3 kPa) and seal the apparatus. After 10 min, record the pressure and visually examine the device for leaks.

5.5.2 Blood compartment integrity

Compliance shall be determined by review of the validation records for the test procedure.

5.5.3 Haemodialyser, haemodiafilter and haemofilter blood compartment ports

Compliance with 4.4.3 shall be determined by inspection. See Figure 1 and Figure 3.

5.5.4 Haemodialyser and haemodiafilter dialysis fluid compartment ports

Compliance with 4.4.4 shall be determined by inspection. See Figure 2.

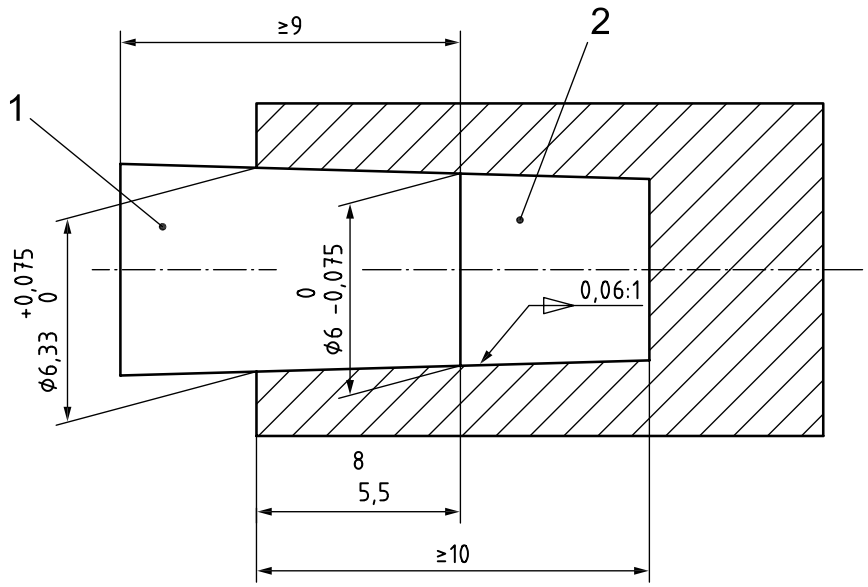
5.5.5 Haemofilter filtrate ports

Compliance with 4.4.5 shall be determined by inspection and shall meet the requirements of Figure 2 or the requirements of ISO 594-2.

5.5.6 Haemoconcentrator blood and filtrate ports

Compliance with 4.4.6 shall be determined by inspection and shall not separate under an axial force of 15 N.

Dimensions in millimetres



Key

1 outer cone

2 inner cone

Figure 3 — Gauge for measuring length of engagement of the male cone of blood inlet and outlet ports

5.6 Performance characteristics

5.6.1 Clearance

5.6.1.1 General

Compliance with 4.5.1 shall be determined as stated below.

5.6.1.2 Test solutions

Perfuse the blood compartment with dialysis fluid, saline, phosphate-buffered saline or water containing one or more of the test substances listed in Table 1.

Perfuse the dialysis fluid compartment of haemodialysers and haemodiafilters with dialysis fluid, saline, phosphate-buffered saline or water.

NOTE The solutions used to perfuse the blood and dialysis fluid compartments should be of similar ionic strength.

Table 1 — Reference concentrations of test solutions

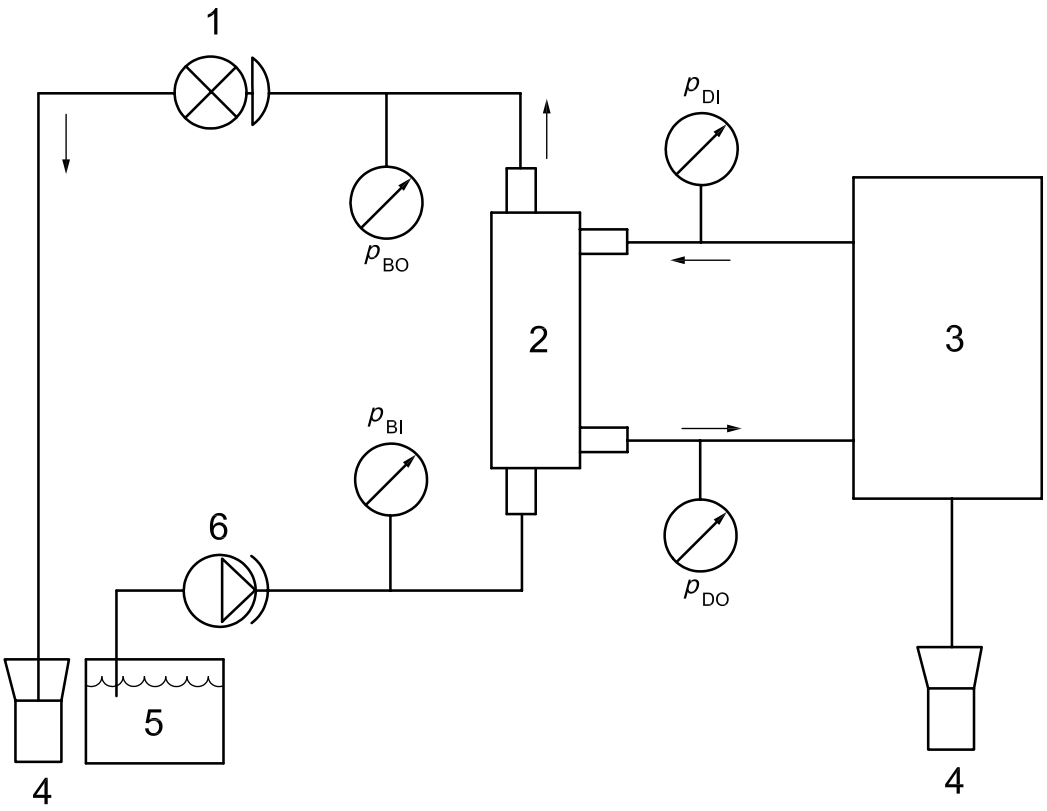
Solute	Molar concentration
Urea, mmol/l	15 to 35
Creatinine, µmol/l	500 to 1 000
Phosphate, mmol/l	1 to 5, adjusted to pH 7,4 ± 0,1
Vitamin B_{12}, µmol/l	15 to 40
NOTE The concentrations of the solutes listed will vary based on the test procedure. The listed solutes are only given as a starting point.	

5.6.1.3 Clearance test procedure

Set up the test circuit as shown in Figure 4. Establish stable conditions (temperature, flow and pressure) for blood and filtrate flows and ensure all air is removed from the haemodialyser or haemodiafilter. Collect test samples after steady state has been reached, over the specified range of blood and dialysis fluid flow rates. The ultrafiltration rate shall be stated for each condition. Analyse samples and calculate clearance in accordance with Equation (1).

NOTE 1 Although Figure 4 shows flow entering the blood compartment at the bottom of the haemodialyser or haemodiafilter, the test can also be performed with flow entering the blood compartment at the top of the haemodialyser or haemodiafilter, provided the flows through the blood and dialysis fluid compartments remain counter-current. The test can also be performed with the haemodialyser or haemodiafilter in the horizontal position, provided that configuration has been shown to produce equivalent results to those obtained with the haemodialyser or haemodiafilter in the vertical position.

NOTE 2 A practical method of confirming the reliability of the measurement is to monitor the mass balance error.



Key

1 pressure control
2 haemodialyser or haemodiafilter
3 dialysis fluid supply system with ultrafiltration controller
4 waste
5 test solution reservoir
6 blood pump
p_{BI} blood pressure, in
p_{BO} blood pressure, out
p_{DI} dialysis fluid pressure, in
p_{DO} dialysis fluid pressure, out

Figure 4 — Diagram of open-loop system for measuring clearance of haemodialyser or haemodiafilter

5.6.1.4 Equation for calculating clearance

The clearance for haemodialysis and haemodiafiltration, K, is calculated using Equation (1).

$$K = \left(\frac{c_{BI} - c_{BO}}{c_{BI}} \right) q_{BI} + \frac{c_{BO}}{c_{BI}} q_F \quad (1)$$

In the equation, it is necessary to use the same units of measurement for c_{BI} and c_{BO}.

where

c_{BI} is the concentration of solute on the blood inlet side of the haemodialyser or haemodiafilter;

c_{BO} is the concentration of solute on the blood outlet side of the haemodialyser or haemodiafilter;

q_{BI} is the blood flow rate at the inlet of the device;

q_F is the filtrate flow rate (ultrafiltration rate).

5.6.2 Sieving coefficient of haemodiafilters, haemofilters and haemoconcentrators

5.6.2.1 General

Compliance with 4.5.2 shall be determined in accordance with the test described below.

5.6.2.2 Test solutions

The test fluid shall be anticoagulated bovine plasma with a protein content of (60 ± 5) g/l or anticoagulated whole blood with a haematocrit of (32 ± 3) % and a plasma protein content of (60 ± 5) g/l.

Perfuse the blood compartment with a test fluid containing one or more of the substances listed in 4.5.2.

5.6.2.3 Test procedure

Set up the test circuit as shown in Figure 5. Establish stable conditions (temperature, flow and pressure) for blood and filtrate flows and ensure all air is removed from the haemodiafilter, haemofilter or haemoconcentrator. Adjust the ultrafiltration rate to cover the manufacturer's specified range. Collect paired test samples of blood and filtrate fluid flows. Calculate sieving coefficient in accordance with Equation (2).

NOTE Although Figure 5 shows flow entering the blood compartment at the bottom of the haemodiafilter, haemofilter or haemoconcentrator, the test can also be performed with flow entering the blood compartment at the top of the haemodiafilter, haemofilter or haemoconcentrator. The test can also be performed with the haemodiafilter, haemofilter or haemoconcentrator in the horizontal position, provided that configuration has been shown to produce equivalent results to those obtained with the haemodiafilter, haemofilter or haemoconcentrator in the vertical position.

5.6.2.4 Equation for sieving coefficient

The sieving coefficient, S, is calculated using Equation (2).

$$S = \frac{2C_F}{(C_{BI} + C_{BO})} \quad (2)$$

where

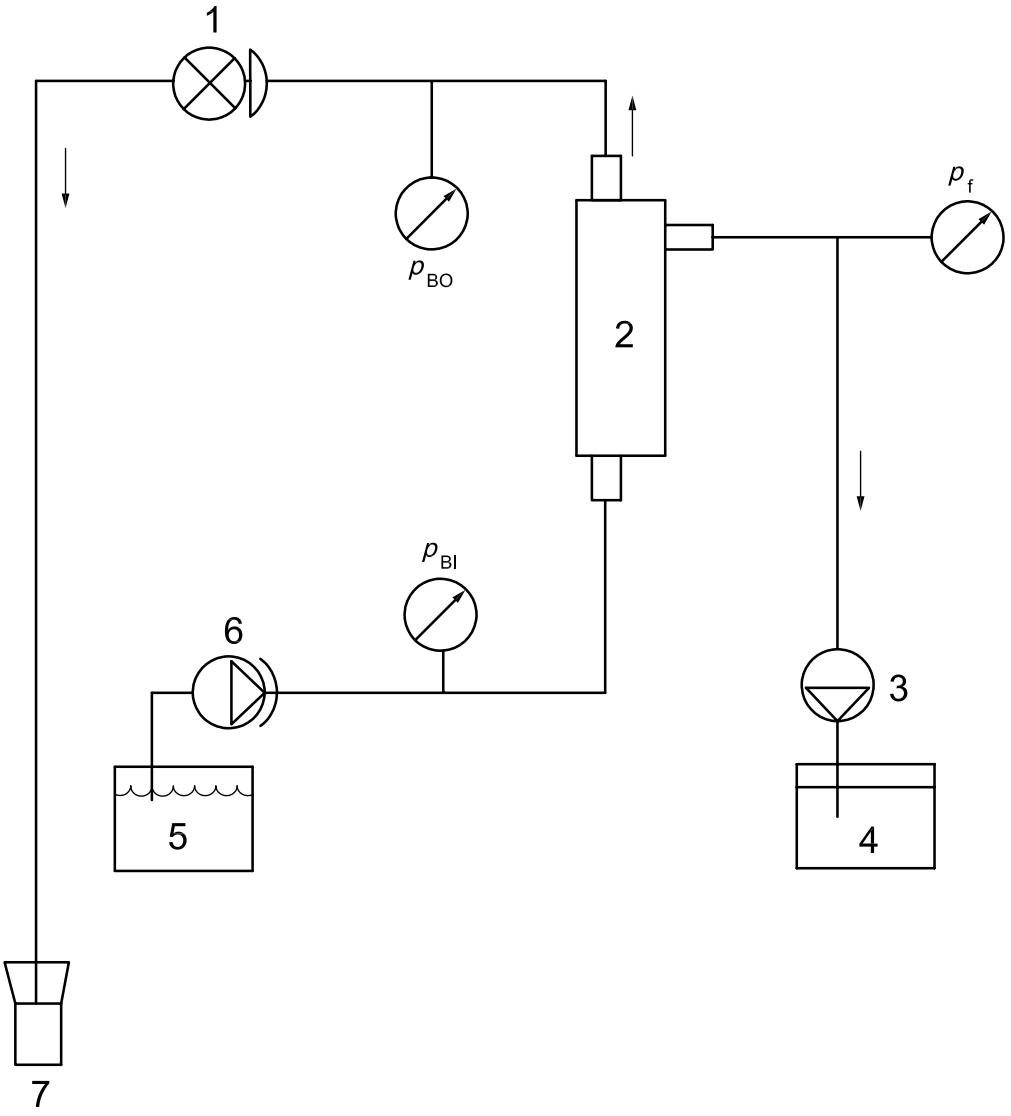
S is the sieving coefficient;

C_{BI} is the concentration of solute on the blood inlet side of the haemodiafilter, haemofilter or haemoconcentrator;

C_{BO} is the concentration of solute on the blood outlet side of the haemodiafilter, haemofilter or haemoconcentrator;

C_F is the concentration of the solute on the filtrate side of the haemodiafilter, haemofilter or haemoconcentrator.

In Equation (2) it is necessary to use the same units of concentration for C_{BI}, C_{BO} and C_F.



Key

1	pressure control	6	blood pump
2	haemodialyser, haemodiafilter, haemofilter or haemoconcentrator	7	waste
3	filtrate pump	p_{BO}	blood pressure, out
4	filtrate	p_{BI}	blood pressure, in
5	test solution reservoir	p_f	filtrate pressure

Figure 5 — Diagram of system for measuring ultrafiltration or sieving coefficients of a haemodialyser, haemodiafilter, haemofilter or haemoconcentrator

5.6.3 Ultrafiltration coefficient

5.6.3.1 Test solution

The test solution for haemodialysers, haemodiafilters and haemofilters shall be anticoagulated bovine or human blood, with a haematocrit of (32 ± 3) % and a protein content of (60 ± 5) g/l. For haemoconcentrators, a test solution of anticoagulated bovine or human blood, with a haematocrit of (25 ± 3) % and a protein content of (50 ± 5) g/l may be used.

No fluid is to perfuse the dialysis fluid or filtrate compartment.

5.6.3.2 Test procedure

Set up the test circuit as shown in Figure 5. Establish stable conditions (temperature, flow and pressure) for blood and filtrate flows and ensure all air is removed from the haemodiafilter, haemofilter or haemoconcentrator. Measure the ultrafiltration flow rate over the manufacturer's specified range. Calculate the ultrafiltration coefficient as the slope of the regression line between filtration flow rate and transmembrane pressure, taking oncotic pressure into account.

NOTE The filtration flow rate is not a linear function of transmembrane pressure above some value of transmembrane pressure. Beyond that point, the filtration flow rate tends to reach a constant value, representing the maximum filtration flow rate for the device.

5.6.4 Volume of the blood compartment

For hollow-fibre devices, the cell volume can be calculated by utilizing the dimensions of the device and the number of fibres in the bundle. If the membrane is known to significantly change dimensions after wetting, the following alternative method should be used.

Alternately, fill the blood compartment with a fluid that is easily removable but that will not pass through the membrane. Measure the volume of the fluid needed to fill the blood compartment. Perform measurements over the specified range of transmembrane pressures. If the blood compartment is noncompliant, the measurement at a single pressure is acceptable.

5.6.5 Pressure drop of the blood compartment

5.6.5.1 General

Compliance with 4.5.5 shall be determined in accordance with the test described below.

5.6.5.2 Test fluids

Fill the blood compartment with a test solution of anticoagulated bovine blood, with a haematocrit of (32 ± 3) % and a protein content of (60 ± 5) g/l or a fluid of similar viscosity, such as aqueous glycerin solution or a xanthan gum/glycerin solution.

Fill the dialysis fluid or filtrate compartment with normal dialysis fluid or saline.

5.6.5.3 Test procedure

Establish blood flow rate. Read the inlet and outlet pressures of the blood compartment. Determine the pressure drop. Repeat over the manufacturer's specified range of blood flow rates.

For plate dialysers, it is also necessary to establish dialysis fluid flow rates and measure pressures and blood flow rates.

5.7 Expiry date

Compliance with 4.6 can be met by accelerated or real time testing for biological safety, sterility and mechanical integrity of the device after storage for a period corresponding to the expiry date.

6 Labelling

6.1 Labelling on the device

The device shall be labelled with at least the following information:

a) the manufacturer's name;

b) the proprietary device name;

c) the manufacturer's identifying code for the device;

d) the lot number;

e) the direction of blood flow and dialysis fluid flow, if applicable;

f) the maximum transmembrane pressure;

g) the expiry date, stated as mm/yyyy or yyyy/mm;

h) the method of sterilization;

i) a statement of single use, if appropriate.

NOTE In all cases above, symbols from ISO 7000 or ISO 15223 can be used where appropriate.

6.2 Labelling on the unit containers

At least the following information shall be visible on or through the unit container:

a) the manufacturer's name and address;

b) the proprietary device name;

c) the manufacturer's identifying code for the device;

d) the lot number;

e) a statement of sterility and non-pyrogenicity; there are three possibilities:

   1) that the entire contents of the package are sterile;

   2) that the fluid pathways (blood and dialysis fluid) are sterile;

   3) that only the blood pathway is sterile;

f) the method of sterilization;

g) the expiry date, stated as mm/yyyy or yyyy/mm;

h) a statement of single use or multiple use;

i) the statement, “Read the instructions before use”;

j) if applicable, a statement that an ultrafiltration control machine is required.

NOTE In all cases above, symbols from ISO 7000 or ISO 15223 can be used where appropriate.

6.3 Labelling on the outer containers

At least the following information shall appear on the outer container:

a) the manufacturer's name and address;

b) the name and address of the distributor, if different from the information given under a), if applicable and in accordance with national requirements;

c) the proprietary device name, description of contents and number of devices contained within the outer container;

d) the manufacturer's identifying code for the device;

e) the lot number;

f) a statement of sterility and non-pyrogenicity;

g) instructions and warnings regarding handling and storage;

h) the expiry date, stated as mm/yyyy or yyyy/mm.

NOTE In all cases above, symbols from ISO 7000 or ISO 15223 can be used where appropriate.

6.4 Accompanying documentation

At least the following information shall be supplied with each outer container:

a) the manufacturer's name and address;

b) the proprietary device name;

c) directions for use:

   1) a statement to follow the machine manufacturer's instructions (if provided) for the orientation of the device in the support;

   2) the positioning of the extracorporeal circuit connection and, if appropriate, the positioning of the dialysis fluid tubing connections;

   3) the recommended priming, rinsing and termination of haemodialysis, haemodiafiltration, haemofiltration or haemoconcentration procedures;

   4) the direction of blood flow, if applicable;

   5) a typical circuit diagram;

   6) the need for anticoagulation and a statement to follow the physician's prescription;

   7) details of any ancillary equipment required;

d) cautions and warnings:

   1) pressure limitations, if any;

   2) dialysis fluid flow rate limitations, if any (applicable only to haemodialysers and haemodiafilters);

   3) blood flow rate limitations, if any;

   4) instructions to rinse the device as recommended before use;

   5) the need for any special equipment;

   6) a list of known adverse reactions;

   7) a list of general and specific contra-indications, such as “Not recommended for paediatric use” and “Do not use on non-de-aerated dialysis fluid delivery systems”;

   8) appropriate warnings and contra-indications of diminished performance if the device is used below certain flow rates, below a certain pressure or in particular orientations (horizontal, vertical, etc.);

e) the manufacturer's identifying code (catalogue number) for the device;

f) a statement of sterility and non-pyrogenicity, and the method of sterilization;

g) a statement of single use or multiple use; if labelled for multiple use, a statement where data supporting multiple use may be obtained (if required by national or regional regulations, the data supporting reuse shall be included in the package insert);

h) performance data for the device shall be included or referred to. Performance data for the device shall include membrane surface area, clearances, sieving coefficient (if the device is intended for convective therapies), ultrafiltration coefficient (k_{uf}), information on the relationship between ultrafiltration rate and transmembrane pressure if the device is intended for convective therapies, blood side pressure drop and blood compartment volume for the device;

   NOTE Performance data should include or make reference to:

   — a statement, if appropriate, that *in vitro* results are likely to differ from *in vivo* results, with an estimate of the magnitude of the difference, if known;

   — a statement, if appropriate, that the performance might change with the duration of observation;

   — the test methods used for determination of performance characteristics.

i) instruction for reprocessing of the haemodialyser, if so labelled, shall include but not be limited to:

   1) instructions for header and o-ring disassembly, cleaning and assembly, if applicable;

   2) recommended cleaning and reprocessing agents and processes;

   3) a method for determining chemical residuals before use;

   4) instructions on performance tests needed prior to reuse of the haemodialyser;

   5) a warning against the use of any agent or process known to adversely affect the haemodialyser;

   6) if labelled for reuse, a statement that the haemodialyser shall only be reused on the same patient;

   7) a statement, if applicable, of the effect of haemodialyser reuse on the performance of the haemodialyser;

j) the generic name and, if applicable, the brand name of the membrane;

NOTE The generic name of the membrane should include the complete chemical name of the membrane material.

k) a general description of the device; this information should include special features such as filtration rates requiring special controllers or adverse effects of bubbles in the dialysis fluid;

l) the connectors recommended for the dialysis fluid ports or filtration port;

m) if blood compartment connectors are not as in Figure 1 and Figure 3, specify the type of blood tubing connectors that are compatible with the device;

n) the generic names of materials of construction of the device intended for direct or indirect contact with blood.

NOTE In all cases above, symbols from ISO 7000 or ISO 15223 can be used where appropriate.

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