INTERNATIONAL STANDARD

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Second edition
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Cardiovascular implants and artificial organs — Haemodialysers, haemodiafilters, haemofilters and haemoconcentrators

Implants cardiovasculaires et organes artificiels — Hémodialyseurs, hémodiafiltres, hémofiltres et hémoconcentrateurs

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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*.

This second edition cancels and replaces the first edition (ISO 8637:1989), which has been technically revised.

Introduction

This International Standard is concerned with devices intended for haemodialysis, haemofiltration, haemodiafiltration and haemoconcentration in humans. The requirements specified in this International Standard will help to ensure their 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 dialysate 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 the standard is voluntary and it does not supersede any national regulation.

Cardiovascular implants and artificial organs — 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 for 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 dialysate,

— 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 8638, *Cardiovascular implants and artificial organs — Extracorporeal blood circuit for haemodialysers, haemodiafilters and haemofilters*

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

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, haemodiafilter, haemofilter or haemoconcentrator 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
dialysate
dialysing fluid
solution which is intended to exchange solutes and/or water in blood during haemodialysis or haemodiafiltration

3.5
dialysate compartment
part of a haemodialyser or haemodiafilter through which dialysate 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 dialysate or filtrate compartment of a haemodialyser, haemodiafilter, haemofilter or haemoconcentrator, due to a pressure gradient 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

3.10
haemodiafilter
device intended to perform haemodiafiltration

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 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
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
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 which is

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

— accompanying a medical device, and is related to identification, technical description and use of the 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
TMP
Differential 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 dialysate 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.

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 in accordance with the manufacturer's instructions for use.

NOTE 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 Nonpyrogenicity

The blood pathway of the device shall be nonpyrogenic. Compliance shall be verified in accordance with 5.4.

4.4 Mechanical characteristics

4.4.1 Structural integrity

When tested in accordance with 5.5.1, haemodialysers, haemodiafilters, haemofilters and haemo-concentrators shall not leak. The device shall be evaluated at

a) 1,5 times the maximum pressure specified, and

b) 1,5 times the recommended sub-atmospheric pressure specified by the manufacturer, not to exceed 700 mmHg or the maximum obtainable sub-atmospheric pressure.

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 times 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.

4.4.4 Haemodialyser and haemodiafilter dialysate compartment ports

The dimensions of the dialysate compartment ports shall be as given in Figure 2. Compliance with this requirement shall be verified according to 5.5.4.

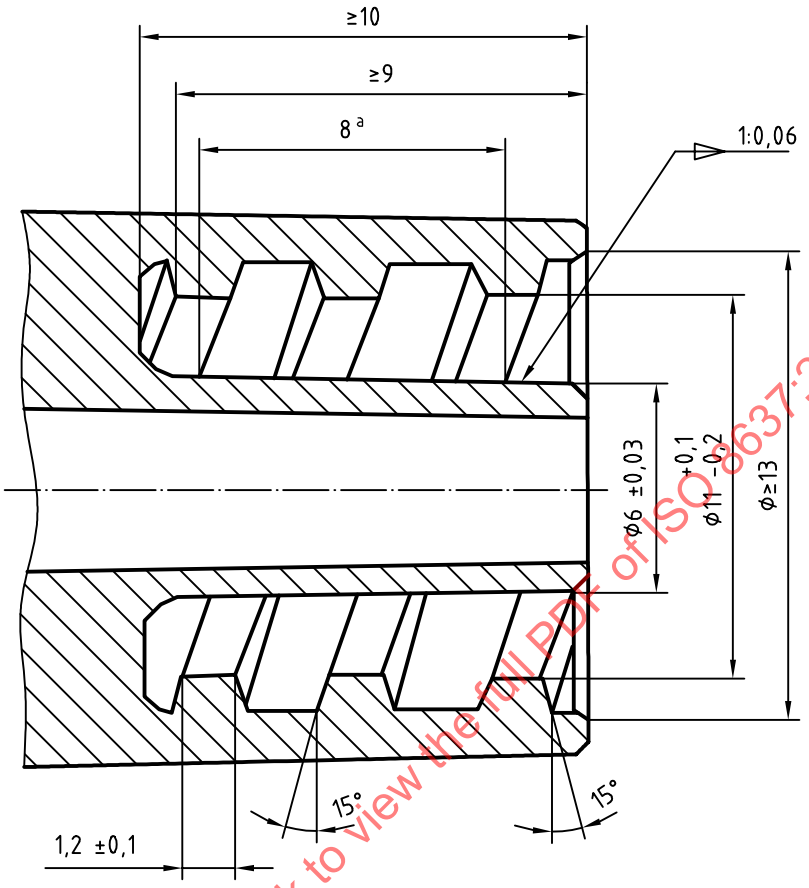
4.4.5 Haemofilter filtrate ports

The filtrate ports of haemofilters shall either comply with Figure 2 or comply with the requirements of the Luer taper 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



[a] Double thread.

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

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 dialysate flowrates shall cover the manufacturer's recommended 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 shall be determined in accordance with 5.6.2. Test conditions shall be as presented by the manufacturer in the labelling.

4.5.3 Filtration rate

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

Dimensions in millimetres

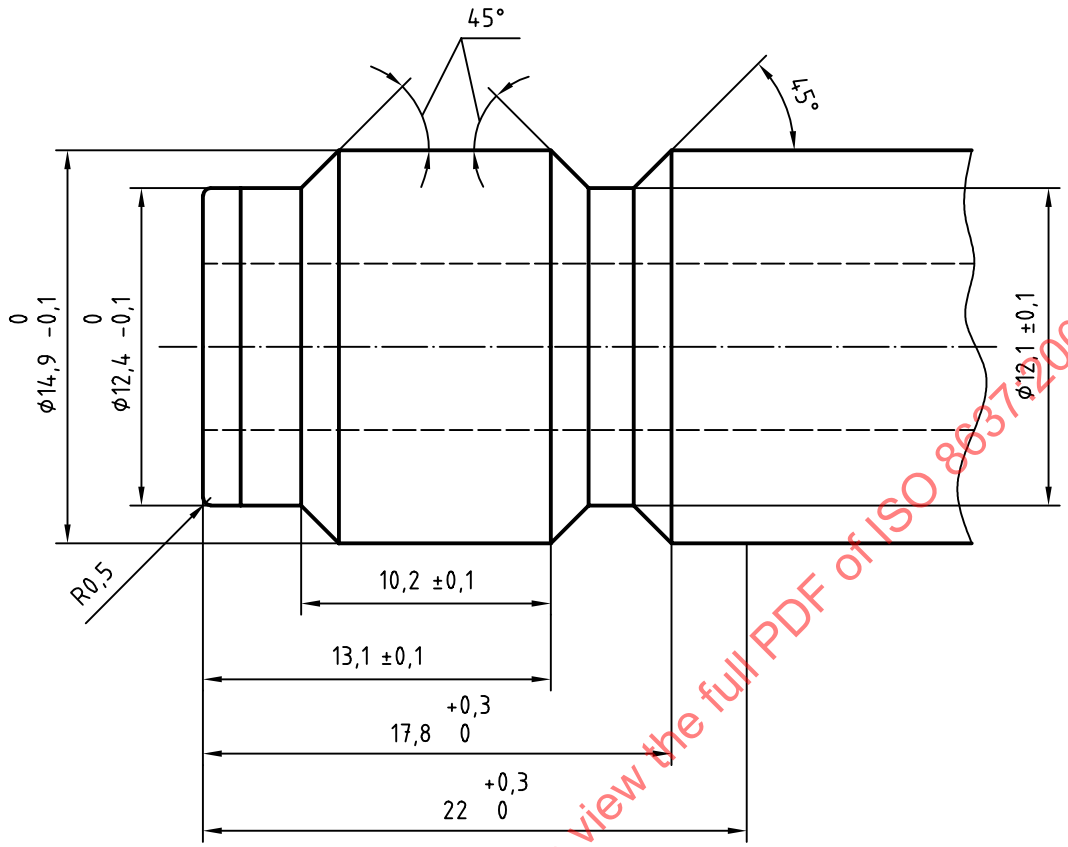


Figure 2 — Main fitting dimensions of dialysate inlet and outlet port

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.

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

4.5.5 Pressure drop

4.5.5.1 Pressure drop of the blood compartment

The pressure drop of the blood compartment shall be determined in accordance with 5.6.5.1.

4.5.5.2 Pressure drop of the dialysate compartment

The pressure drop of the dialysate compartment shall be determined in accordance with 5.6.5.2.

4.6 Expiration date

Biological safety, sterility and mechanical integrity of the device shall be proven after storage for a period corresponding to the expiration 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 may alter its performance. If labelled for multiple uses, devices shall be tested for clearances and ultrafiltration rate after reprocessing according to the manufacturer's instructions, in order to characterize the effects of the recommended cleaning agent and germicide on membrane performance.

Sample devices for testing 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 document are reference tests. Other test methods may be used, provided it can be shown that they are of comparable precision and reproducibility.

The test systems shown do not indicate all the necessary details of practicable test apparatus. The design and construction of actual test systems and their establishment 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 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 those 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 those described in 5.3, 5.4, 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 the requirements in 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 Nonpyrogenicity

Compliance with the requirement in 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 times the manufacturer's recommended pressure and seal the apparatus. After 10 min, record the pressure and examine the device visually for leaks.

5.5.1.3 Sub-atmospheric 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 times the manufacturer's recommended pressure, unless that sub-atmospheric pressure exceeds 700 mmHg or is not specified; in that case, apply a sub-atmospheric pressure of 700 mmHg and seal the apparatus. After 10 min, record the pressure and examine the device visually 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 the requirement specified in 4.4.3 shall be determined by inspection. See Figure 1 and Figure 3.

5.5.4 Haemodialyser or haemodiafilter dialysate compartment ports

Compliance with the requirement specified in 4.4.4 shall be determined by inspection. See Figure 2.

5.5.5 Haemofilter filtrate ports

Compliance with the requirements of 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 the requirement specified in 4.4.6 shall be determined by inspection and shall not separate under an axial force of 15 N.

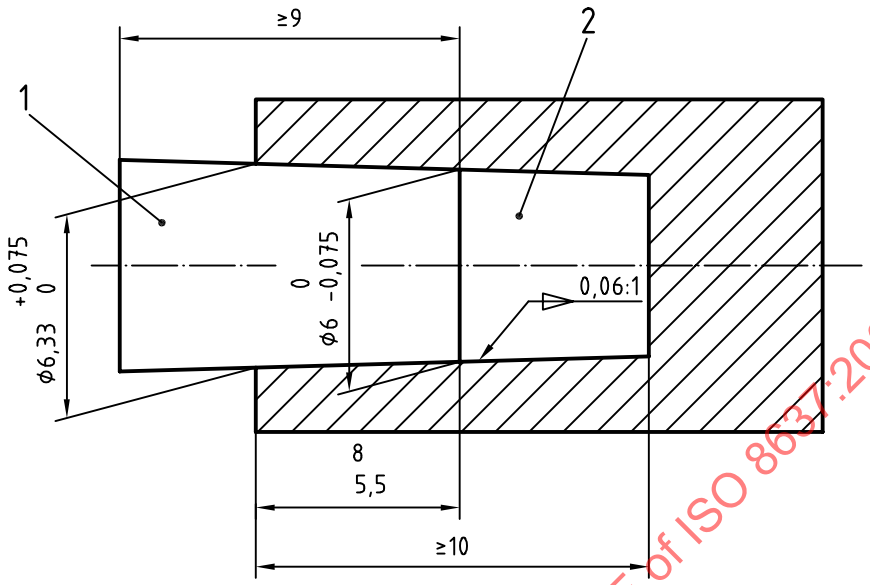
5.6 Performance characteristics

5.6.1 Clearance

5.6.1.1 General

Compliance with 4.5.1 shall be determined as stated below.

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 connectors

5.6.1.2 Test solutions

Perfuse the blood compartment with a normal dialysate containing one or more of the test substances listed in Table 1 below.

Perfuse the dialysate compartment of haemodialysers and haemodiafilters with dialysate.

NOTE The molar concentrations of the solutes listed in Table 1 vary depending on the test procedure. The listed solutes are only given as a starting point.

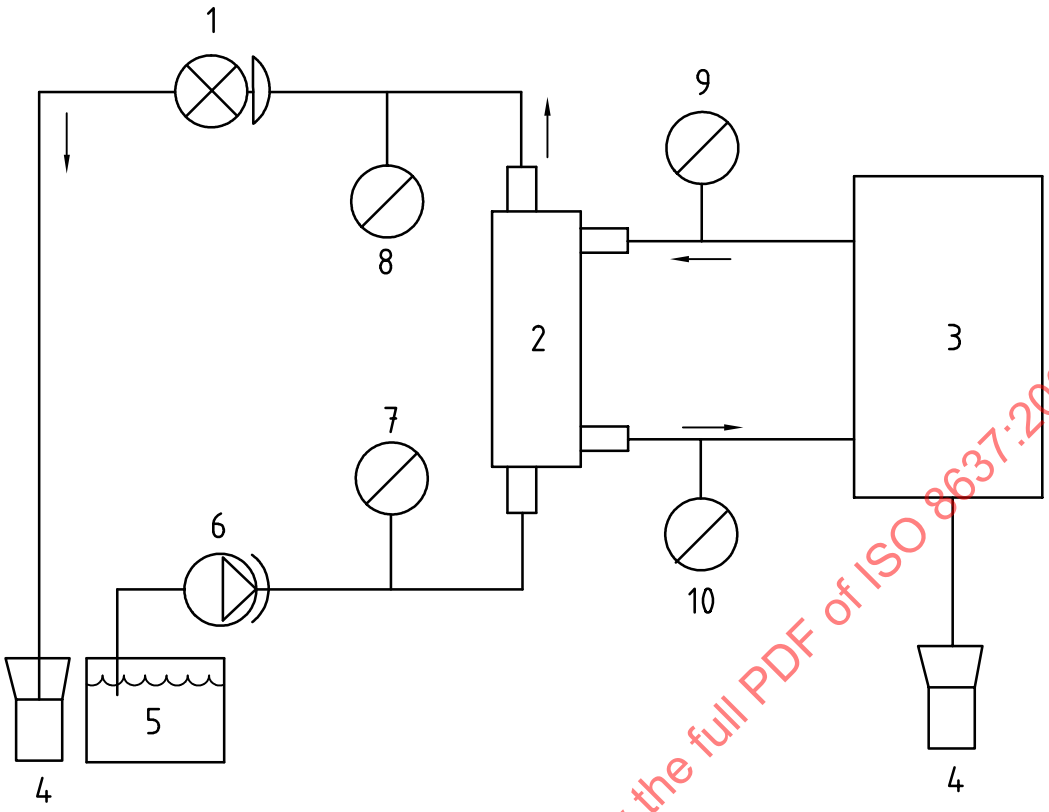
Table 1 — Reference molar concentrations of test solutions

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

5.6.1.3 Clearance test procedure

Set up the test circuit as shown in Figure 4. Establish stable blood and dialysate flowrates. Make certain that the temperature, pressures and ultrafiltration rates are stable. Collect test samples after steady state has been reached, over the specified range of blood and dialysate flowrates. The ultrafiltration rate shall be stated for each condition. Analyse samples and calculate clearance according to the formula in 5.6.1.4.

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



Key

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

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

5.6.1.4 Formula for calculating clearance

For haemodialysis and haemodiafiltration, calculate the clearance, K, 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 concentration 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 flowrate at the inlet of the device;

q_F is the filtrate flowrate (ultrafiltration rate).

5.6.2 Sieving coefficient for haemofilters, haemodiafilters and haemoconcentrators

5.6.2.1 General

Compliance with 4.5.2 shall be determined according to the test below.

5.6.2.2 Test solutions

The preferred test fluid is anticoagulated bovine plasma with a 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 (temperature, flowrate and pressure) blood and filtrate flows. Adjust the ultrafiltration rate to cover the manufacturer's specified range. Collect paired test samples of blood and filtrate fluid flows. Calculate sieving coefficient according to the formula in 5.6.2.4.

5.6.2.4 Formula for sieving coefficient

$$S = \frac{2c_F}{c_{BI} + c_{BO}}$$

where

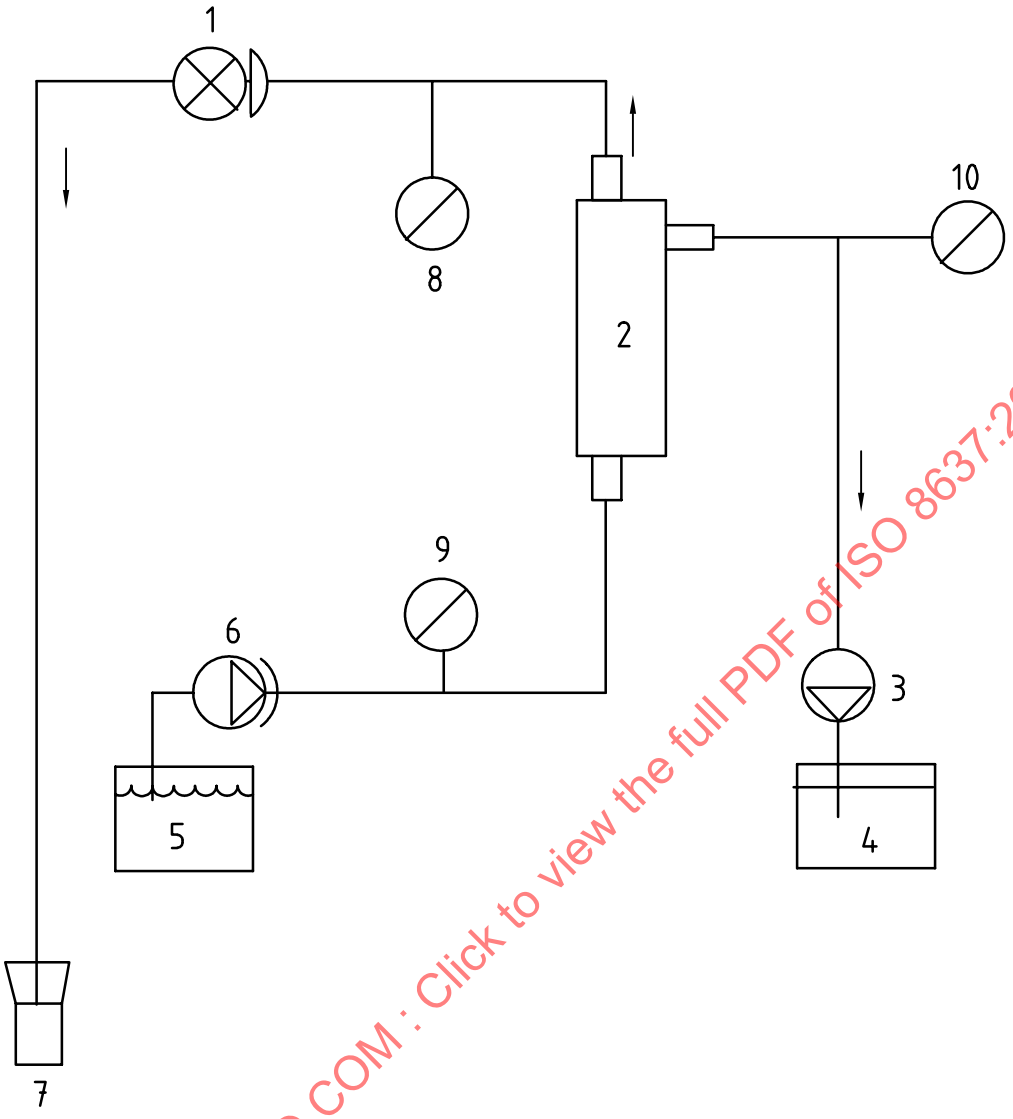
S is the sieving coefficient;

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

In the equation it is necessary to use the same units of concentration for c_{B1}, c_{BO} and c_F.



Key

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

Figure 5 — Diagram of system for measuring ultrafiltration or sieving coefficients of parallel-plate or hollow-fibre haemodialyser, haemodiafilter, haemofilter or haemoconcentrator

5.6.3 Filtration rate

5.6.3.1 Test solution

The test solution shall be anticoagulated bovine or human blood, with a haematocrit of (32 ± 2) % and a protein content of (60 ± 5) g/l.

No fluid shall perfuse the dialysate or filtrate compartment.

5.6.3.2 Test procedure

Set up the test circuit as shown in Figure 5. Establish stable (temperature, flowrate and pressure) blood and filtrate flows. Measure the ultrafiltration flowrate over the manufacturer's specified range. The sequence of measurement shall be from minimum to maximum transmembrane pressure.

5.6.4 Volume of the blood compartment

For hollow-fibre dialysers, the cell volume can be calculated from the dimensions of the dialyser and the number of fibres in the bundle. If the membrane is known to significantly change dimensions after wetting, the alternative method below should be used.

Alternatively, fill the blood compartment with a fluid which is easily removable but 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, measurement at a single pressure is acceptable.

5.6.5 Pressure drop

5.6.5.1 Pressure drop in the blood compartment

5.6.5.1.1 General

Compliance with 4.5.5.1 shall be determined using the following test method.

5.6.5.1.2 Test fluids

Fill the blood compartment with a test solution of anticoagulated bovine blood, with a haematocrit of (32 ± 2) % and a protein content of (60 ± 5) g/l or a fluid of similar viscosity.

Fill the dialysate or filtrate compartment with normal dialysate.

5.6.5.1.3 Test procedure

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

For plate dialysers, it is also necessary to establish dialysate flowrates and measure pressures and blood flowrates.

5.6.5.2 Pressure drop in the dialysate compartment

5.6.5.2.1 Test fluids

Fill the dialysate compartment with a test solution of normal dialysate.