International Standard

ISO 8637-1

Second edition
2024-05

Extracorporeal systems for blood purification —

Part 1: Haemodialysers, haemodiafilters, haemofilters and haemoconcentrators

Systèmes extracorporels pour la purification du sang —

Partie 1: 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.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO document should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

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Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT), see www.iso.org/iso/foreword.html.

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

This second edition cancels and replaces the first version of this document (ISO 8637-1:2017), which has been technically revised.

The main changes are as follows:

— terms and definitions have been aligned with those defined in other parts of the ISO 8637 series;

— additional figures relating to gauges used to test dimensional compliance have been added;

— test methods have been revised and an example of a test method for endotoxin transfer measurement has been added;

— requirements for accompanying documentation have been revised.

A list of all parts in the ISO 8637 series can be found on the ISO website.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

This document is concerned with devices intended for haemodialysis, haemodiafiltration, haemofiltration and haemoconcentration in humans. If such a device is used with an extracorporeal circuit, the dimensions of the blood ports and filtrate ports have been specified to ensure compatibility of the device with the extracorporeal blood circuit specified in ISO 8637-2. The design and dimensions have been selected to minimize the risk of leakage of blood and the ingress of air.

The requirements specified in this document will help to ensure safety and satisfactory function.

It was not found practicable to specify materials of construction. This document therefore requires only that materials which have been used 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 performance characteristics together with their methods of measurement have been revised and updated to take into consideration developments in technology that have occurred since the publication of the previous edition of this document.

Extracorporeal systems for blood purification —

Part 1: Haemodialysers, haemodiafilters, haemofilters and haemoconcentrators

1 Scope

This document specifies requirements and test methods for haemodialysers, haemodiafilters, haemofilters and haemoconcentrators, hereinafter collectively referred to as "the device", for use in humans.

This document does not apply to:

— extracorporeal blood circuits;

— plasmafilters;

— haemoperfusion devices;

— vascular access devices;

— blood pumps;

— systems to prepare, maintain or monitor dialysis fluid;

— systems or equipment intended to perform haemodialysis, haemodiafiltration, haemofiltration or haemoconcentration;

— reprocessing procedures and equipment.

NOTE 1 Requirements for extracorporeal blood circuits for haemodialysers, haemodiafilters and haemofilters are specified in ISO 8637-2.

NOTE 2 Requirements for plasmafilters are specified in ISO 8637-3.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements 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 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*

ISO 11737-2, *Sterilization of health care products — Microbiological methods — Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process*

ISO 11607-1, *Packaging for terminally sterilized medical devices — Part 1: Requirements for materials, sterile barrier systems and packaging systems*

ISO 11607-2, *Packaging for terminally sterilized medical devices — Part 2: Validation requirements for forming, sealing and assembly processes*

ISO 14971, *Medical devices — Application of risk management to medical devices*

ISO 17664-1, *Processing of health care products — Information to be provided by the medical device manufacturer for the processing of medical devices — Part 1: Critical and semi-critical medical devices*

ISO 20417, *Medical devices — Information to be supplied by the manufacturer*

ISO 80369-7:2021, *Small-bore connectors for liquids and gases in healthcare applications — Part 7: Connectors for intravascular or hypodermic applications*

3 Terms and definitions

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

ISO and IEC maintain terminology databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at https://www.electropedia.org/

3.1
blood compartment
part of a *haemodialyser* (3.16), *haemodiafilter* (3.14), *haemofilter* (3.18) or *haemoconcentrator* (3.13) through which blood is intended to pass

3.2
blood compartment volume
volume which is needed to fill the blood compartment

Note 1 to entry: For hollow fibre devices, the blood compartment volume includes the volume of the hollow fibres plus the headers.

3.3
blood compartment connector
blood connector
cone type connector to permit the entry and exit of blood and to connect the device to blood tubing sets

Note 1 to entry: Historically the term blood port was used.

3.4
clearance
volume of a solution from which a solute is completely removed per unit time

3.5
convection
transport of a solvent across a semipermeable membrane resulting from a pressure differential across the membrane

Note 1 to entry: Convective solute transport supplements diffusive transport as a result of “solute drag” whereby solutes contained in the solvent are co-transported with the solvent.

3.6
convective therapy
form of renal replacement therapy that removes uremic toxins from blood either by convection solely or by a combination of diffusion and convection through a semipermeable membrane

Note 1 to entry: Convective therapies remove toxins from the blood by removing fluid from the device in excess of that required to achieve the patient’s target fluid balance, thereby requiring infusion of replacement fluid into the patient’s blood. In contrast, haemodialysis removes fluid from the device only to correct the patient’s fluid weight gain realized between dialysis treatments.

Note 2 to entry: Haemofiltration and haemodiafiltration are types of convective therapies.

Note 3 to entry: Haemoconcentrators are fluid removal devices used during cardiac surgery.

3.7
dialysis fluid
aqueous fluid containing electrolytes and, usually, buffer and glucose, which is intended to exchange solutes with blood during *haemodialysis* (3.17) or *haemodiafiltration* (3.15)

Note 1 to entry: The term "dialysis fluid" is used throughout this document to mean the fluid (made from dialysis water and concentrates) which is delivered to the haemodialyser or haemodiafilter by a dialysis fluid delivery system. Phrases such as "dialysate", "dialysis solution" or "dialysing fluid" can be used in place of dialysis fluid.

Note 2 to entry: 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" or "effluent".

Note 3 to entry: Dialysis fluid does not include pre-packaged fluids used in some renal replacement therapies.

3.8
dialysis fluid compartment
part of a *haemodialyser* (3.16) or *haemodiafilter* (3.14) through which *dialysis fluid* (3.7) is intended to pass

3.9
dialysis fluid connector
dialysate connector
connector forming part of the device to permit the passage of dialysis fluid through the device and to link the device to equipment producing the dialysis fluid

3.10
diffusion
transport of solutes across a semipermeable membrane, caused by a concentration gradient

3.11
filtrate
fluid removed from the blood across the semipermeable membrane contained in a *haemodialyser* (3.16), *haemodiafilter* (3.14), *haemofilter* (3.18) or *haemoconcentrator* (3.13), due to a pressure gradient (including the contributions of both hydrostatic and oncotic pressures) across the semipermeable membrane

Note 1 to entry: In a haemodialyser and haemodiafilter, the fluid removed is mixed with dialysis fluid flowing through the device.

3.12
haemoconcentration
convective process with the purpose of removing excess plasma water from the patient's blood volume, that has been expanded by physiologic fluid, as typically required during cardiac surgery

3.13
haemoconcentrator
device intended to perform *haemoconcentration* (3.12)

3.14
haemodiafilter
device intended to perform *haemodiafiltration* (3.15)

3.15
haemodiafiltration
HDF
process whereby concentrations of water-soluble substances in a patient's blood and an excess of fluid of a patient are corrected by a simultaneous combination of *haemodialysis* (3.17) and *haemofiltration* (3.19)

Note 1 to entry: Diffusive solute removal is achieved using a dialysis fluid stream as in haemodialysis. Enhanced convective solute removal is achieved by adding ultrafiltration in excess of that needed to achieve the desired weight loss; fluid balance is maintained by the infusion of a replacement solution into the blood circuit either before (pre-dilution haemodiafiltration) or after (post-dilution haemodiafiltration) or a combination of the two (mixed dilution haemodiafiltration).

[SOURCE: IEC 60601-2-16:2018, 201.3.209, modified — Note 1 to entry has been added.]

3.16
haemodialyser
device intended to perform *haemodialysis* (3.17)

3.17
haemodialysis
HD
process whereby concentrations of water-soluble substances in a patient's blood and an excess of fluid of a patient are corrected by bidirectional diffusive transport and ultrafiltration across a semipermeable membrane separating the blood from the dialysis fluid

Note 1 to entry: This process typically includes fluid removal by filtration. This process is usually also accompanied by diffusion of substances from the dialysis fluid into the blood.

[SOURCE: IEC 60601-2-16:2018, 201.3.209]

3.18
haemofilter
device intended to perform *haemofiltration* (3.19)

3.19
haemofiltration
HF
process whereby concentrations of water-soluble substances in a patient’s blood and an excess of fluid of a patient are corrected by convective transport via ultrafiltration and partial replacement by a substitution fluid resulting in the required net fluid removal

[SOURCE: IEC 60601-2-16:2018, 201.3.211]

Note 1 to entry: In haemofiltration, there is no dialysis fluid stream.

3.20
labelling
written, printed, graphic or electronic matter that is affixed to a device (haemodialyser, haemodiafilter, haemofilter or haemoconcentrator) or any of its containers or wrappers, or accompanies a device and which is related to identification, technical description and use of that device, but excluding shipping documents

3.21
sieving coefficient
ratio of a solute concentration in the filtrate to the simultaneous concentration of the same solute in the plasma

3.22
transmembrane pressure
TMP
p_{TM}
mean pressure exerted across a semipermeable membrane

Note 1 to entry: 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.

3.23
ultrafiltration
UF
pressure driven process employing a hydraulic pressure gradient applied to a semipermeable membrane

Note 1 to entry: In haemodialysis treatment, ultrafiltration generally refers to the removal process used to remove excess fluid from the patient.

3.24
ultrafiltration coefficient
permeability of the device to plasma water

Note 1 to entry: The ultrafiltration coefficient is generally expressed in millilitres per hour per millimetre of mercury.

3.25
ultrafiltration rate
UFR
filtrate flow rate from the blood compartment to the dialysis fluid compartment caused by a pressure gradient or pressure differential across the membrane measured as volume per time

Note 1 to entry: Ultrafiltration rate is expressed in ml/min or l/h.

4 Requirements

4.1 Biological safety and haemocompatibility

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 and the state of sterility of the device shall comply with the manufacturer's statement [see 7.2 h)].

Compliance shall be verified in accordance with 5.3.

4.3 Non-pyrogenicity

The blood pathway of the device shall be non-pyrogenic and the state of non-pyrogenicity of the device shall comply with the manufacturer's statement [see 7.2 h)].

Compliance shall be verified in accordance with 5.4.

4.4 Mechanical characteristics

4.4.1 Structural integrity

The device external casing shall be capable of withstanding a positive pressure of 1,5 times of the manufacturer's recommended maximum pressure above atmospheric pressure and a negative pressure not exceeding 66,7 kPa (500 mmHg) below atmospheric pressure, when tested in accordance with 5.5.1.

4.4.2 Blood compartment integrity

When exposing the blood compartment of the device to a validated test procedure performed at 1,5 times of 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 Blood compartment connectors of haemodialysers, haemodiafilters and haemofilters

Except where the device and the extracorporeal blood circuit are designed as an integral system, the dimensions of the blood compartment connectors shall be as given in Figure 1 and Table 1.

Compliance with this requirement shall be verified in accordance with 5.5.3.2.

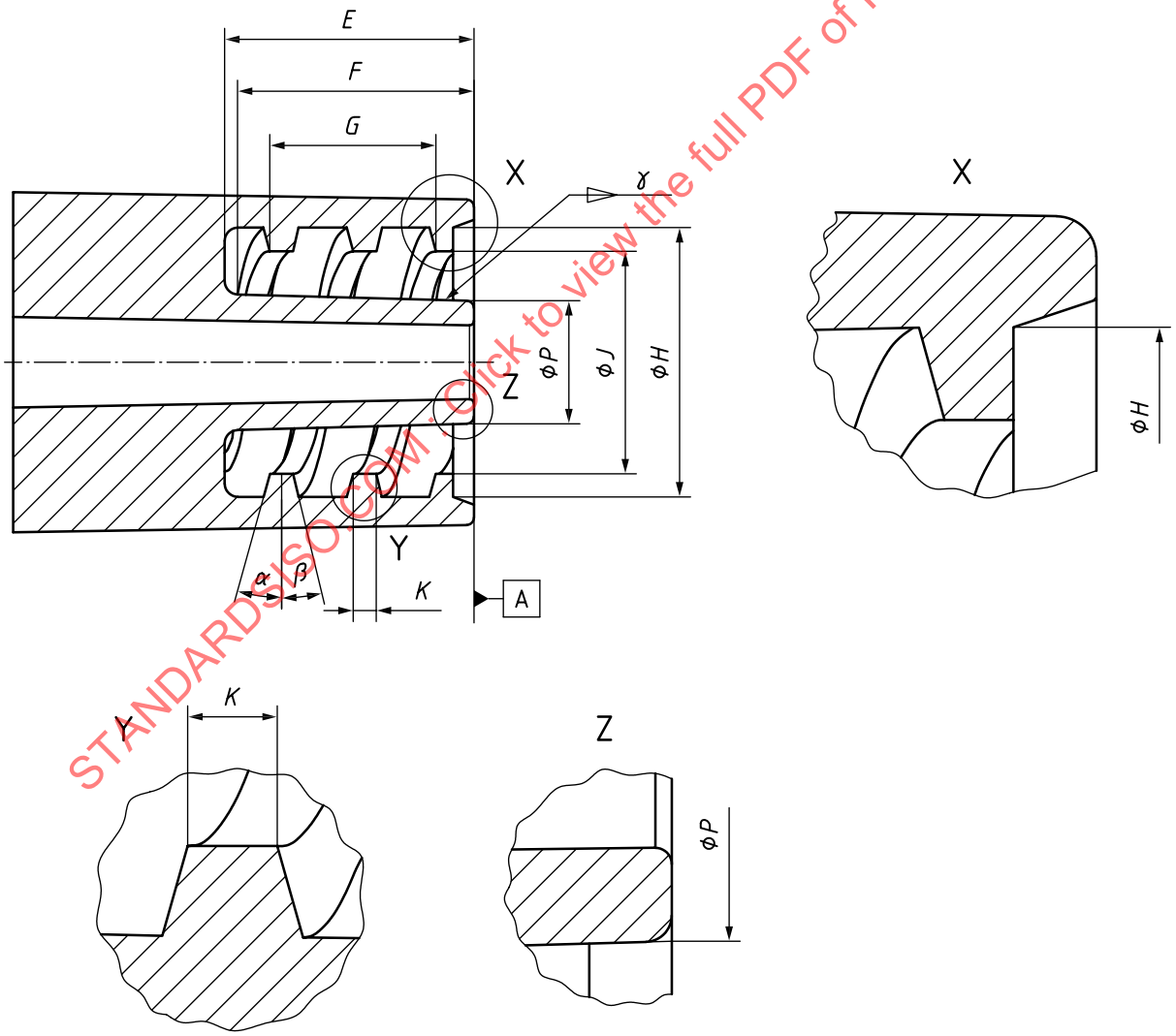


Figure 1 — Cone blood inlet and outlet blood compartment connector of haemodialysers, haemodiafilters or haemofilters

Table 1 — Dimensions of the blood compartment connector

	E mm	*F* mm	*G*[a] mm	*H* mm	*J*[b] mm	*K*[c] mm	*P*[d] mm	*α* °	*β* °	*γ*
Minimum	10 or more	9 or more	8	13 or more	10,8	0,85	5,97	—	—	6:100
Nominal					11,0	1,10	6,00	15	15	
Maximum					11,3	1,35	6,03	—	—	

Key

E length of tapered region
F length of tapered region
G thread pitch
H root diameter
J crest diameter
K thread crest width
P cone diameter
α angle of thread
β angle of thread
γ dimension taper rate

[a] Double thread pitch.
[b] Altered upper tolerance to accommodate different components and materials.
[c] Revised dimension and tolerances based on existing manufacturing practice.
[d] Cone's plane of reference: square A. This dimension is measured as a projection on the front face. See Figure 1 (Z).

4.4.4 Dialysis fluid compartment connectors of haemodialysers and haemodiafilters

Except where the haemodialyser or haemodiafilter and the dialysis fluid circuit are designed as an integral system, the dimensions of the dialysis fluid compartment connectors shall be as given in Figure 2 and Table 2.

Compliance with this requirement shall be verified in accordance with 5.5.3.3.

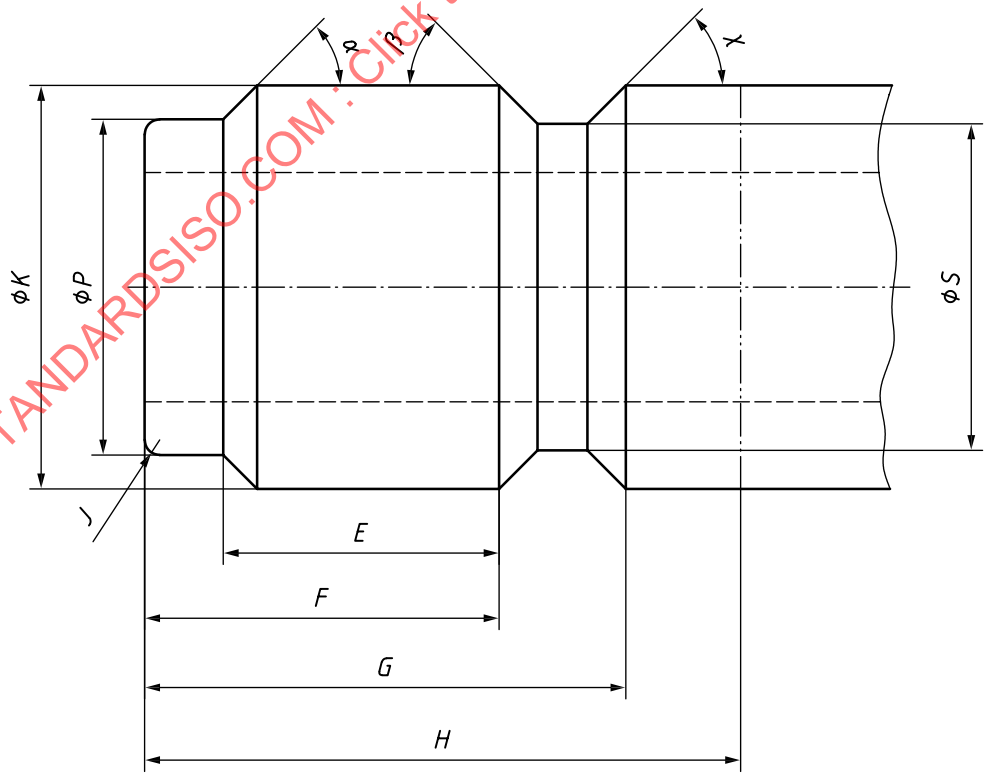


Figure 2 — Main fitting dimensions of the dialysis fluid inlet and outlet connector

Table 2 — Main fitting dimensions of the dialysis fluid inlet and outlet connector

	E mm	*F* mm	*G* mm	*H*[a] mm	*J* mm	*K* mm	*P*[b] mm	*S*	*α* °	*β* °	*X* °
Minimum	10,1	13,0	17,8	22 or more	0,5	14,8	12,3	12,0			
Nominal	10,2	13,1	17,8			14,9	12,4	12,1	45	45	45
Maximum	10,3	13,2	18,1			14,9	12,5	12,2			

Key

E testing length
F reference length
G testing length range
H cone diameter
J cone diameter
K cone diameter
P diameter
S diameter
α angle of sealing surface
β angle of sealing surface
X angle of sealing surface

[a] It defines the necessary length and diameter for engagement with the socket connectors of dialysis fluid circuit.

[b] Together with *α*, it defines diameter of the sealing surface for the dialysis fluid connectors.

4.4.5 Filtrate connectors of haemofilters

Except where the haemofilter and the filtrate circuit are designed as an integral system, the filtrate connectors of haemofilters shall follow either

a) the design of Figure 2, or

b) the Luer lock connector design of ISO 80369-7:2021, Figures B.1 and B.3.

Compliance with this requirement shall be verified in accordance with 5.5.3.4.

4.4.6 Blood and filtrate connectors of haemoconcentrators

4.4.6.1 Blood connectors

The blood and filtrate connectors of haemoconcentrators shall allow for a secure connection to the tubing which is to be used with the device.

Non-locking connectors shall not separate under an axial force of 25 N applied for 15 s.

Except where the device and the extracorporeal blood circuit are designed as an integral system, the dimensions of the blood compartment connectors shall be as given in Figure 1 and Table 1.

Dimensional compliance shall be determined using any one or combination of the following: digital contact measurement instruments, optical measurement, three-dimensional X-ray imaging, analogue gauges or another validated method. The dimensional compliance assessment may involve destructive methods to gain access to features for measurement.

Compliance with this requirement shall be verified in accordance with 5.5.3.5.

4.4.6.2 Filtrate connectors

Except where the haemoconcentrators are designed as an integral system, the filtrate connector design shall follow

a) the design of Figure 2, or

b) the non-locking connection for direct attachment of the tubing, or

c) the Luer lock connector design of ISO 80369-7:2021, Figures B.1 and B.3.

If non-locking connectors are used, they shall not separate under an axial force of 25 N applied for 15 s.

Compliance with this requirement shall be verified in accordance with 5.5.3.5.

4.5 Performance characteristics

4.5.1 Solute clearance for 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, urea mass transfer area coefficient (KoA) results are included.

4.5.2 Sieving coefficients for haemodialysers, haemodiafilters, haemofilters and haemoconcentrators

For haemodialysers, haemodiafilters and haemofilters, the sieving coefficients (SCs) for albumin, inulin, and β_2-microglobulin or myoglobin shall be determined in accordance with 5.6.2.

Additionally, the following middle molecular weight proteins are of known clinical interest and represent a range of molecular weights across the middle molecular spectrum. The manufacturer can choose to report the SC for either these compounds or other middle molecular proteins, or both, to provide performance characteristics if the SC for these proteins is larger than or equal to 0,1:

— kappa free light chains (κ-FLC, 23 kDa);

— complement factor D (CFD, 24 kDa);

— alpha 1-microglobulin (α1-M, 33 kDa);

— chitinase-3-like-protein 1 (YKL-40, 40 kDa);

— lambda free light chains (λ-FLC, 45 kDa).

For haemoconcentrators, the sieving coefficient for albumin shall be determined in accordance with 5.6.2.

4.5.3 Ultrafiltration rate

The ultrafiltration rate shall be determined if the device is intended for convective therapies in accordance with 5.6.3.

4.5.4 Ultrafiltration coefficient

The ultrafiltration coefficient shall be determined in accordance with 5.6.4.

4.5.5 Blood compartment volume

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

If the blood compartment volume is stable or constant over the clinical range of pressures, a single measurement is sufficient. If the blood compartment volume varies with pressure, the blood compartment volume over the clinical range of pressures shall be established.

4.5.6 Blood compartment pressure drop

The pressure drop of the blood compartment shall be determined in accordance with 5.6.6.

4.5.7 Endotoxin transfer of haemodialysers and haemodiafilters

The manufacturer shall determine that the risk to the patient is acceptable regarding pyrogenic response due to endotoxin transfer between the dialysis fluid pathway and the blood fluid pathway during preparation and therapy, and considering the results of endotoxin transfer testing.

Compliance with this requirement shall be verified in accordance with 5.6.7.

4.6 Expiry date

The biological safety, sterility, performance data and mechanical integrity of the device shall be proven after storage for a period corresponding to the expiry date. The expiry date can be established with validated accelerated stability studies and shall be confirmed by real time aging data.

Compliance shall be verified in accordance with Clause 6.

5 Test methods

5.1 General

The requirements specified in Clause 4 shall be determined prior to marketing a new type of device and shall be re-evaluated after changes in the device that can alter its performance.

If labelled for multiple uses, devices shall be tested for structural integrity, biological safety and performance after reprocessing in accordance with the manufacturer's instructions to characterize the effects of the recommended cleaning agent and germicide on membrane performance.

For the tests, device sample size shall be risk based and shall be capable of demonstrating that the test results meet the full range of specifications of the manufacturer with statistical confidence.

Configuration of the disposable samples used for the tests shall be representative of the final production configuration, including sterilization.

Measurements shall be made in vitro at (37 ± 1) °C. When the relationship between variables is nonlinear, 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 they have been validated and shown to be precise and reproducible.

The test systems shown do not indicate all the necessary details of a practicable test apparatus. The design and construction of actual test systems and the establishment of actual test systems shall also address 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, which are carried out prior to the marketing of a new device or when changes are made to the device or its manufacturing processes. Others are of a quality control nature, which are repeated on a regular basis according to quality management system requirements.

5.2 Biological safety and haemocompatibility

The biological safety of haemodialysers, haemodiafilters, haemofilters and haemoconcentrators pathways 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 in accordance with 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 sterilization process that has been validated in accordance with ISO 11737-2.

5.4 Non-pyrogenicity

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

NOTE ISO 10993-11 does not specifically address the requirements for endotoxin mediated pyrogenicity test methods but makes reference to ANSI/AAMI ST72.

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 test methods given in 5.5.1.2 and 5.5.1.3.

5.5.1.2 Positive pressure test

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

Alternately, a constant air pressure (1,5 times of the manufacturer’s recommended maximum pressure) can be applied and the device can be submerged in water to test for air leakage.

5.5.1.3 Negative pressure test

Completely fill the device with degassed water at (37 ± 1) °C. Seal all connectors except the connector to which pressure is applied. Place the device under sub-atmospheric pressure of 1,5 times of the manufacturer's recommended maximum pressure, unless that sub-atmospheric pressure exceeds 66,7 kPa (500 mmHg) or

is not specified. In that case, apply a sub-atmospheric pressure of at least 66,7 kPa (500 mm Hg). Seal the apparatus. After 10 min, record the pressure and visually examine the device for leaks.

Alternately, a constant negative air pressure of 66,7 kPa (500 mmHg) can be applied and the device can be submerged in water to test for water leakage.

5.5.2 Blood compartment integrity

Compliance to 4.4.2 shall be determined by review of the validation records for the test procedure.

5.5.3 Connectors

5.5.3.1 General

All connectors shall provide a safe connection. In the case of blood connectors, to ensure a safe connection, excessive leakage of air from the outside or loss of blood to the environment shall be avoided and in the case of dialysis fluid connectors, the ingress of air or the leakage of dialysis fluid shall be avoided.

The degree of acceptable leakage rate, minimum separation force, minimum separation torque and maximum connection torque shall be defined in accordance with the manufacturer's risk management process. Boundary parameters used in tests such as torques, connection forces and disconnection forces as well as holding times, ambient temperatures, must be considered and defined as part of the manufacturer's assessment for the use of the product.

5.5.3.2 Blood compartment connectors of haemodialysers, haemodiafilters and haemofilters

Compliance with 4.4.3 shall be determined by dimensional inspection meeting the requirements of Figure 1 and Table 1.

Dimensional compliance shall be determined using any one or combination of the following: digital contact measurement instruments, optical measurement, three-dimensional X-ray imaging, analogue gauges or other validated method.

Functional compliance is demonstrated by tests and acceptance criteria derived from the risk management process. Where appropriate, reference may be made to ISO 80369-20, which specifies test methods to evaluate the performance of small bore connectors in healthcare applications.

The analogue gauge described in Figures 3 to 5 is suitable for determining conformity to the Table 1 specification for cone diameter, P, and dimensional taper rate, γ. Figure 3 indicates the required dimensions and tolerances of the gauge. Figure 4 illustrates a socket reference connector to measure the cone. The gauge shown in Figure 3 conforms to the dimensions and tolerances of the socket reference connector. Figure 5 illustrates a cone engaged with the gauge meeting the specifications for cone diameter and taper rate of Table 1 within the acceptance window "a".

NOTE Dimensional assessment can involve destructive methods to gain access to features for measurement.

5.5.3.3 Dialysis fluid compartment connectors of haemodialysers and haemodiafilters

Compliance shall be determined by dimensional inspection meeting the requirements of Figure 2 and Table 2 and determined using any one or combination of: digital contact measurement instruments, optical measurement, three-dimensional X-ray imaging, analogue gauges or another validated method.

Functional compliance is demonstrated by tests and acceptance criteria derived from the risk management process.

NOTE Dimensional assessment can involve destructive methods to gain access to features for measurement.

5.5.3.4 Filtrate connectors of haemofilters

For connectors having the design of Figure 2, compliance shall be determined by dimensional inspection and demonstrated by meeting the requirements of Figure 2 and Table 2, and shall be determined using any one or combination of: digital contact measurement instruments, optical measurement, three-dimensional X-ray imaging, analogue gauges or another validated method.

Functional compliance is demonstrated by tests and acceptance criteria derived from the risk management process. Where appropriate, reference can be made to ISO 80369-20, which specifies test methods to evaluate the performance of small bore connectors in healthcare applications.

For connectors having the design of a Luer lock connector described in ISO 80369-7, compliance shall be determined by dimensional inspection meeting the requirements of ISO 80369-7.

Dimensional compliance shall be determined using any one or combination of: digital contact measurement instruments, optical measurement, three-dimensional X-ray imaging, analogue gauges or another validated method.

For the required tests, a reference connector representing the relevant worst-case dimensions of corresponding female port shall be used.

NOTE Dimensional assessment can involve destructive methods to gain access to features for measurement.

5.5.3.5 Blood and filtrate connectors for haemoconcentrators

For connectors of Figure 1 design, compliance shall be determined by dimensional inspection and demonstrated by meeting the requirements of Figure 1 and Table 1. For connectors of the type shown in Figure 2, compliance shall be determined by dimensional inspection and demonstrated by meeting the requirements of Figure 2 and Table 2.

Non-locking connections shall not separate under an axial force of 25 N applied for 15 s.

For connectors having the design of Luer lock connectors of ISO 80369-7, compliance shall be determined by dimensional inspection meeting the requirements of ISO 80369-7.

Dimensional compliance shall be determined using any one or combination of the following: digital contact measurement instruments, optical measurement, three-dimensional X-ray imaging, analogue gauges or another validated method.

Functional requirements, tests and acceptance criteria shall be used as defined by the manufacturer's risk assessment and used as inspection and test conditions. Where appropriate, reference may be made to ISO 80369-20 which specifies test methods to evaluate the performance of small bore connectors in healthcare applications.

For connectors of the type shown in Figure 1, the analogue gauge described in Figures 3 to 5 is suitable for determining conformity to the Table 1 specification for cone diameter, P, and dimensional taper rate, γ. Figure 3 and Table 3 indicate the required dimensions and tolerances of the gauge. Figure 4 and Table 4 illustrate a socket reference connector and its dimensions for measuring the cone. The gauge of Figure 3 conforms to the dimensions and tolerances of the socket reference connector. Figure 5 illustrates a cone engaged with the gauge meeting the specifications for cone diameter and taper rate of Table 1 and within the acceptance window “a”.

NOTE Dimensional assessment can involve destructive methods to gain access to features for measurement.

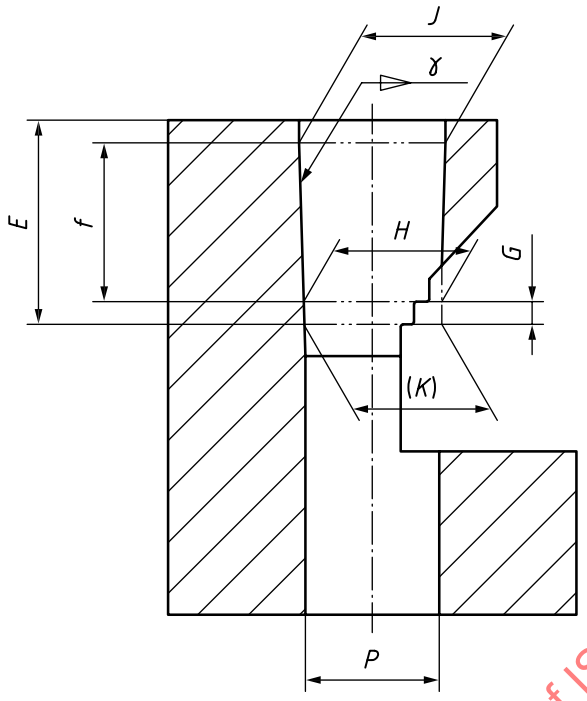


Figure 3 — Socket conical gauge for testing the blood connector cone

Table 3 — Dimensions of the socket conical gauge

	E mm	*f* mm	*G* mm	*H* mm	*J* mm	(*K*) mm	*P* mm	*γ*
Minimum	9	—	0,990	6,025	6,444	5,970	—	6:100
Nominal	—	7	1,000	6,030	6,449		—	
Maximum	—	—	1,000	6,030	6,449		5,9	

Key

E testing length
f reference length
G testing length range
H cone diameter
J cone diameter
(*K*) cone diameter
P diameter
γ taper

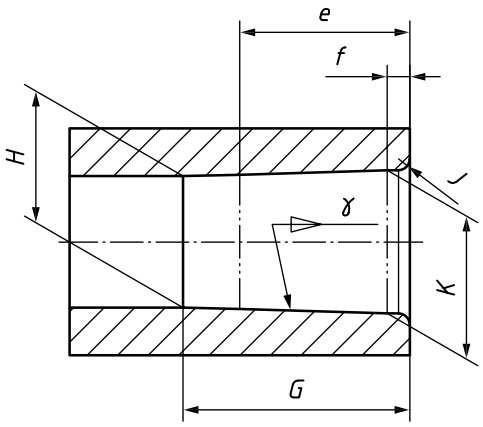


Figure 4 — Socket reference connector for testing the blood connector cone

Table 4 — Dimensions of the socket reference connector

	e mm	*f* mm	*G* mm	*H* mm	*J* mm	*K* mm	*γ*
Minimum	—	—	10	5,911	—	6,301	6:100
Nominal	7,5	1	—	5,916	—	6,306	
Maximum	—	—	—	5,916	0,5	6,306	

Key

e reference length for limit of engagement with cone connector

f reference length for *K*

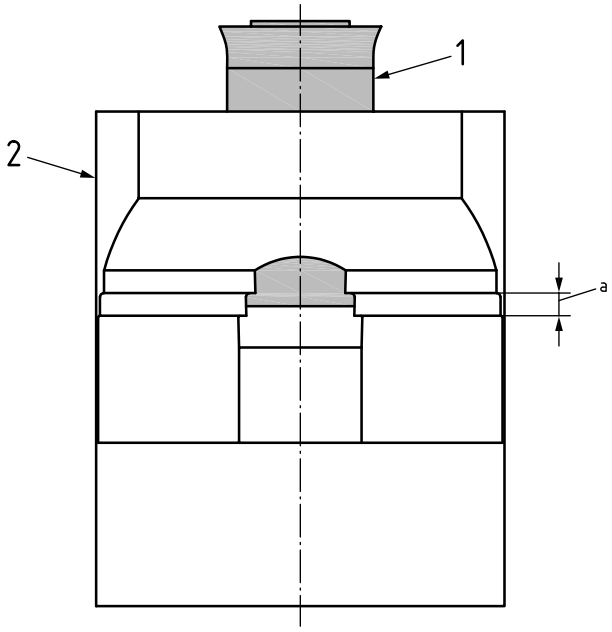
G minimal length of cone

H taper cone

J radius

K taper cone

γ taper



Key

1 cone

2 gauge

[a] Testing dimension range.

Apply the gauge to the conical connector with a total axial force of 5 N, without the use of torque. Remove the axial load.

Figure 5 — Socket conical gauge for testing the cone blood connector

5.6 Performance characteristics

5.6.1 Solute clearance of haemodialysers and haemodiafilters

5.6.1.1 General

Compliance with 4.5.1 shall be determined in accordance with 5.6.1.

5.6.1.2 Test solution

Perfuse the blood compartment with dialysis fluid, saline, phosphate-buffered saline or water containing one or more of the test substances listed in Table 5.

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

NOTE The solution used to perfuse the blood and dialysis fluid compartments are intended to be of similar ionic strength.

Table 5 — Reference concentrations of test solutions

Solute	Molar concentration
Urea[a]	15 mmol/l to 35 mmol/l
Creatinine	500 µmol/l to 1 000 µmol/l
Phosphate	1 mmol/l to 5 mmol/l, adjusted to pH 7,4 ± 0,1
Vitamin B_{12}	15 µmol/l to 40 µmol/l

[a] Sodium is similar to urea regarding molecular weight, diffusive and convective behaviour. Sodium chloride measurements can be used as a surrogate for urea. If sodium is used as a surrogate this should be indicated in the product literature.

NOTE The concentrations of the solutes listed will vary based on the test procedure. The listed solutes molar concentrations are for guidance only.

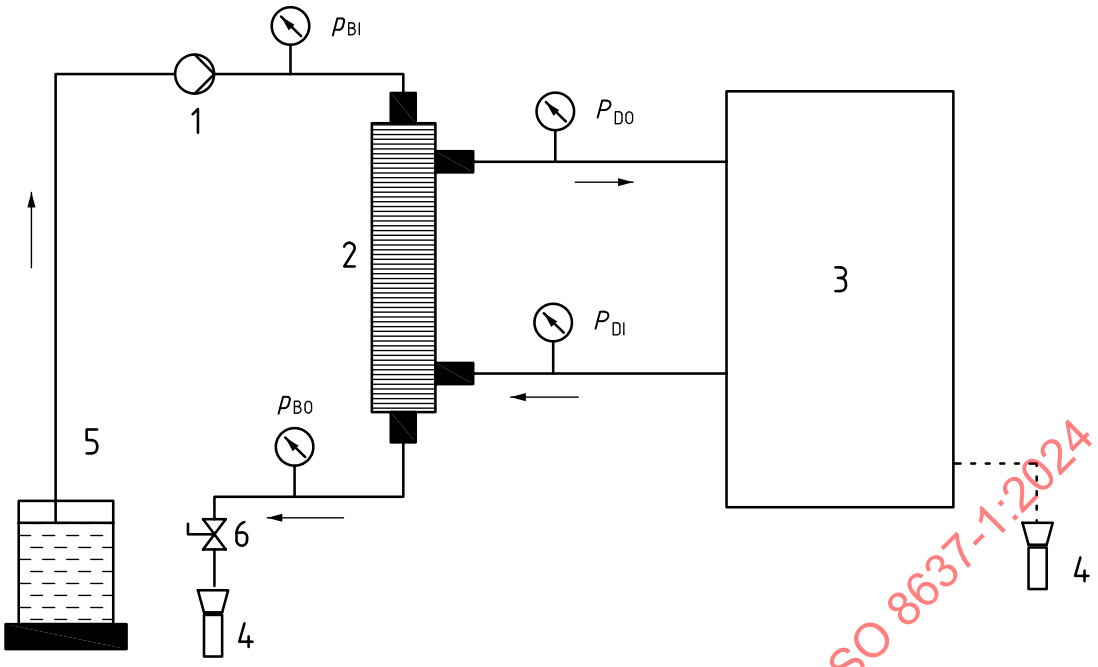
5.6.1.3 Test procedure for the determination of clearance

Set up the test circuit as shown in Figure 6 (open loop system). Establish stable conditions (temperature, flow and pressure) for blood, dialysis fluid and filtrate flow rates, and ensure all air is removed from the haemodialyser or haemodiafilter. Collect test samples after a steady-state of concentrations, temperature and flow rates has been reached over the specified range of flow rates. The ultrafiltration rate shall be stated for each condition. Analyse samples and calculate clearance in accordance with Formula (1). If the test system includes a substitution fluid line, ensure that sampling for c_{BI} in the blood circuit is taken before the point of infusion of the substitution fluid in pre-dilution and sampling for c_{BO} in the blood circuit is taken after the point of infusion of the substitution fluid at post-dilution.

NOTE 1 Although Figure 6 shows flow entering the blood compartment at the top of the haemodialyser or haemodiafilter, the test can also be performed with flow entering the blood compartment at the bottom 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 mass balance error.

NOTE 3 Haemodialysers require specific characterization under relevant conditions if they are used in certain modalities of continuous renal replacement therapy (CRRT) where the dialysis fluid flow rate, q_D, is lower than the blood flow rate, q_B.



Key

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

NOTE For the measurement of clearance during haemodiafiltration, an infusion line for the substitution fluid can exist.

Figure 6 — Diagram of an open-loop system for the measurement of the clearance of a haemodialyser or haemodiafilter

5.6.1.4 Calculation of clearance

The clearance for haemodialysis and haemodiafiltration, K, can be calculated using Formula (1):

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

where

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

c_{BO} is the concentration of solute at 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).

NOTE In Formula (1), q_F is defined as the ultrafiltration rate. According to 3.23, the ultrafiltration rate comprises all fluid flow across the membrane driven by the pressure differential. If the test system includes a line for substitution fluid, only the net ultrafiltration rate (flow rate of excess fluid removal) has to be considered in Formula (1) for q_F.

If $q_D < q_B$, such as for some modalities of CRRT, the clearance may be calculated using Formula (2):

$$K = \left(\frac{c_{DO}}{c_{BI}} \right) q_{DO} \quad (2)$$

where

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

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

c_{DO} is the concentration of solute at the dialysis fluid outlet side of the haemodialyser or haemodiafilter;

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

q_{DO} is the dialysis fluid flow rate at the dialysis fluid outlet of the haemodialyser or haemodiafilter;

q_F is the filtrate flow rate (ultrafiltration rate).

NOTE In Formulae (1) and (2), the same units of measurements are required for c_{BI}, c_{BO} and c_{DO}.

5.6.2 Sieving coefficient of haemodialysers, haemodiafilters, haemofilters and haemoconcentrators

5.6.2.1 General

Compliance with 4.5.2 shall be determined in accordance with the test described in 5.6.2.

5.6.2.2 Test solution

The test fluid shall be anticoagulated human or bovine plasma with a protein concentration 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.

NOTE Dilution or haemoconcentration is permitted in order to adjust protein concentration and to obtain the prescribed concentration of (60 ± 5) g/l.

5.6.2.3 Test procedure for the determination of the sieving coefficient

Set up the test circuit as shown in Figure 7 in either a single pass [Figure 7 b)] or re-circulating [Figure 7 b)] flow configuration. Prior to testing, prepare the devices in accordance with the manufacturers' instructions and ensure that all air has been removed from the circuit. The temperature of the test solution shall be maintained at (37 ± 1) °C throughout the procedure.

During preparation and priming, discard the priming fluid to ensure that the total protein concentration of the plasma remains in the range of (60 ± 5) g/l. Verify that the flow rates, pressure and temperatures comply with manufacturer's instructions and remain stable throughout the procedure. Record data during the procedure. To permit the calculation of the sieving coefficient, draw samples at the blood inlet connector and blood outlet connector of the devices and from the filtrate.

Calculate the sieving coefficient in accordance with Formula (3).

NOTE Although Figure 7 shows flow entering the blood compartment at the bottom of the device, the test can also be performed with flow entering the blood compartment at the top of the device. The test can also be performed with the device in the horizontal position, provided that configuration has been shown to produce equivalent results to those obtained with the device in the vertical position.

5.6.2.4 Calculation of the sieving coefficient

The sieving coefficient, S, of the haemodialyser, haemodiafilter, haemofilter or haemoconcentrator is calculated using Formula (3):

$$S = \frac{2c_F}{(c_{BI} + c_{BO})} \tag{3}$$

where

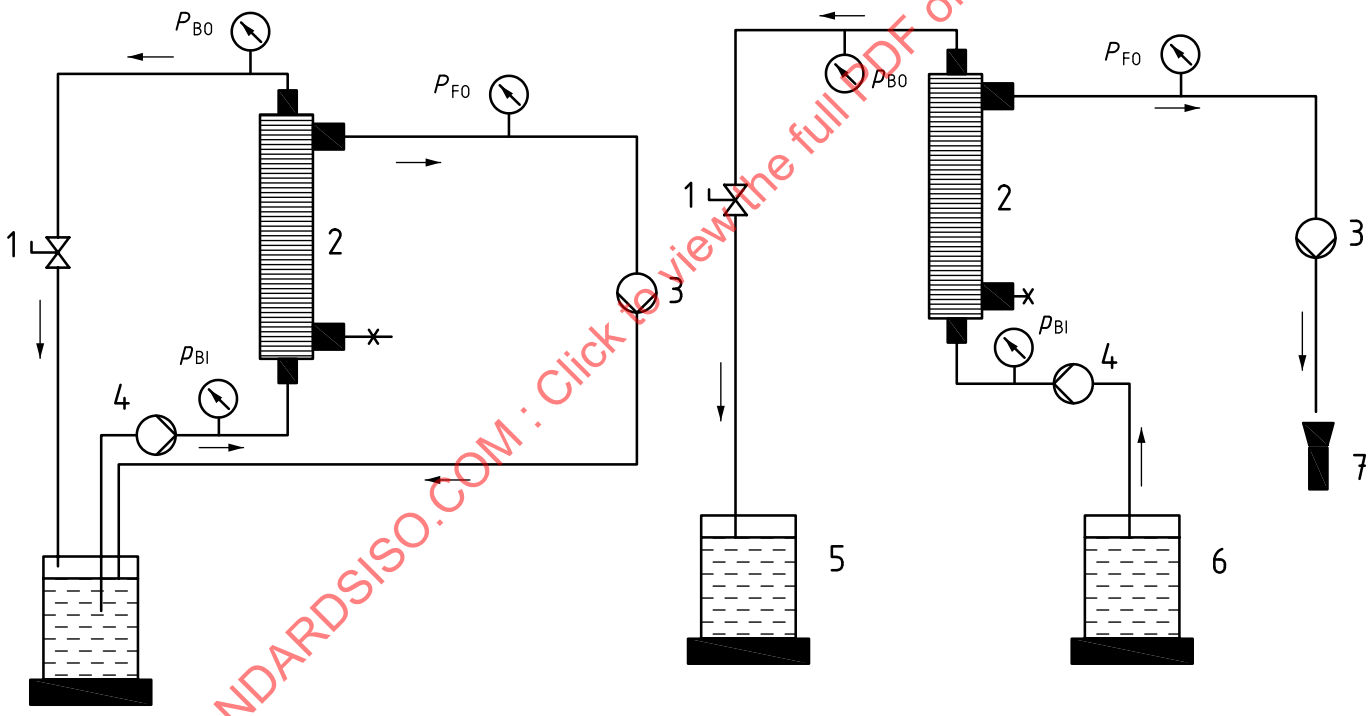
S is the sieving coefficient;

c_{BI} is the concentration of solute at the blood inlet side of the haemodialyser haemodiafilter, haemofilter or haemoconcentrator;

c_{BO} is the concentration of solute at the blood outlet side of the haemodialyser haemodiafilter, haemofilter or haemoconcentrator;

c_F is the concentration of the solute at the filtrate side of the haemodialyser haemodiafilter, haemofilter or haemoconcentrator.

In Formula (3), it is necessary to use the same units of concentration for c_{BI}, c_{BO} and c_F.



a) Recirculating (closed loop) system **b) Single pass (open loop) system**

Key

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

Figure 7 — Diagram of systems for the measurement of the ultrafiltration and sieving coefficients of a haemodialyser, haemodiafilter, haemofilter or haemoconcentrator

5.6.3 Ultrafiltration rate

5.6.3.1 Test solution

The test solution for the determination of ultrafiltration rate of haemodiafilters and haemofilters shall be anticoagulated bovine or human blood, with a haematocrit of (32 ± 3) % and a protein concentration 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 concentration 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 for the determination of the ultrafiltration rate

Prepare the device in accordance with the device's instructions for use to ensure removal of air. Set up the test circuit as shown in Figure 7 in either the single pass [see Figure 7 b)] or recirculating [see Figure 7 a)] flow configuration. Measure the relationship between ultrafiltration rate (UFR) and transmembrane pressure (TMP) from low UFR to the maximum reachable UFR point over the manufacturer's specified blood flow range. The range can require adjustment for smaller surface area devices to ensure a comparable accuracy.

When measuring the pressure differential across the membrane, a correction can be required depending on the orientation of the device and the position of the pressure sensors. A correction to the transmembrane pressure arising from the oncotic pressure shall be made.

NOTE The relationship between UFR and TMP can deviate from linearity at a high TMP and attain a maximum value which remains constant despite increasing transmembrane pressure. This plateau represents the maximum filtration flow rate for the device.

5.6.4 Ultrafiltration coefficient

5.6.4.1 Test solution

The test solution for the perfusion of the blood compartment for haemodialysers, haemodiafilters and haemofilters shall be anticoagulated bovine or human blood, with a haematocrit of (32 ± 3) % and a protein concentration 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 concentration of (50 ± 5) g/l can be used.

5.6.4.2 Test procedure for the determination of the ultrafiltration coefficient

Prepare the device in accordance with the device's instructions for use to ensure the removal of air. Set up the test circuit as shown in Figure 7 in either the single pass [see Figure 7 b)] or recirculating [see Figure 7 a)] flow configuration. Establish stable conditions (temperature, flow and pressure) for blood and filtrate flows. Measure the relationship between UFR and TMP for at least four data points within 1 ml/min/m^2 to 30 ml/min/m^2 and calculate the slope over the linear portion of the curve to obtain the ultrafiltration coefficient.

NOTE For smaller surface area devices, scaling the range of measurements can be necessary to ensure accuracy.

5.6.5 Blood compartment volume

For hollow-fibre devices, the blood compartment volume can be calculated by utilizing the dimensions 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 blood compartment volume with a liquid that is easily removable but will not pass through the membrane. Measure the volume needed to fill the blood compartment.

If the volume of the blood compartment of the device varies with pressure, perform the measurements over a specified range of transmembrane pressures, corresponding to anticipated clinical pressures.

5.6.6 Blood compartment pressure drop

5.6.6.1 General

Compliance with 4.5.6 shall be determined in accordance with the test described in 5.6.6.

5.6.6.2 Test fluids

Fill the blood compartment with a test solution of anticoagulated bovine or human blood, with a haematocrit of (32 ± 3) % and a protein concentration of (60 ± 5) g/l.

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

5.6.6.3 Test procedure for the determination of the pressure drop

Establish the blood flow rate. Measure and record 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 to measure the pressures in the dialysis fluid compartment.

5.6.7 Endotoxin transfer of haemodialysers and haemodiafilters

5.6.7.1 General

Compliance with 4.5.7 shall be verified by inspection of records that a risk assessment has been performed in accordance with ISO 14971 considering the results of endotoxin transfer testing.

5.6.7.2 Test procedure for the determination of the endotoxin transfer

The device shall be challenged using water, saline or dialysis fluid having an endotoxin concentration equal to or greater than the highest level allowed in use, as specified in ISO 23500-5.

Transfer by both diffusion and convection, and consider other potential risk factors.

A sample method is given in Annex A.

6 Expiry date

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

7 Labelling

7.1 Labelling on the device

The device label shall contain the following information:

a) the manufacturer's name;

b) the proprietary device name;

c) the manufacturer’s identifying code (such as the catalogue or model number) for the device;

d) the batch, lot or serial number designation;

e) the direction of blood flow and dialysis fluid flow, if applicable (colour coding can be used to distinguish between inlet to the device and outlet from the device);

f) the maximum transmembrane pressure;

g) the expiry date, stated as mm/yyyy, yyyy/mm or yyyy-mm-dd, where yyyy represents the year, mm the month and dd the day;

h) the method of sterilization;

i) a statement of single use, if appropriate.

NOTE Where symbols exist as shown in either ISO 7000 or ISO 15223-1, or both, these can be used as an alternative.

7.2 Labelling on 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 device proprietary name;

c) the manufacturer’s identifying code (such as the catalogue number or model number) for the device;

d) the batch lot or serial number designation;

e) the expiry date, stated as mm/yyyy, yyyy/mm or yyyy-mm-dd, where yyyy represents the year, mm the month and dd the day;

f) the method of sterilization;

g) a statement of single use, if appropriate;

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

   1) the entire contents of the package are sterile;

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

   3) only the blood pathway is sterile;

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

j) if applicable, a statement that the device must be used with a dialysis machine incorporating ultrafiltration control.

NOTE Where symbols exist as shown in either ISO 7000 or ISO 15223-1, or both, these can be used as an alternative.

7.3 Labelling on the outer containers

At least the following information shall appear on the outer container which generally contains a number of devices:

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;

   NOTE 1 National requirements can apply.

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

d) the manufacturer's identifying code (such as the catalogue number or model number) for the device;

e) the batch, lot or serial number designation;

f) a statement of sterility and non-pyrogenicity;

g) instructions and warnings regarding handling and storage;

h) the expiry date, stated as mm/yyyy, yyyy/mm or yyyy-mm-dd, where yyyy represents the year, mm the month and dd the day;

i) the statement “If the carton is damaged, check the products contained carefully, do not use if the product container is damaged”.

NOTE 2 Where symbols exist as shown in either ISO 7000 or ISO 15223-1, or both, these can be used as an alternative.

7.4 Information to be given in the accompanying documentation

Accompanying documentation shall comply with ISO 20417 and be placed in the outer container in which the devices are shipped. It should include the product specification and the instructions for use in a form of a booklet or leaflet. At least one such booklet or leaflet shall be placed in each outer container.

If the accompanying documentation is available in an electronic version, details of how to access the information shall be provided by the manufacturer.

At least the following information shall be given:

a) the manufacturer's name and address;

b) the device proprietary 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 and dialysis fluid 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 and prime 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, e.g. “Not recommended for paediatric use” and “Do not use on non-de-aerated dialysis fluid delivery systems”;