International Standard

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Second edition
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Extracorporeal systems for blood purification —

Part 3: Plasmafilters

Systèmes extracorporels pour la purification du sang —

Partie 3: Filtres pour plasma

Reference number
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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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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 edition (ISO 8637-3:2018), 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 a gauge to test dimensional compliance of connectors have been added;

— test methods for measurement of the sieving coefficient and haemolytic characteristics have been revised;

— requirements for accompanying documentation have been revised and extended to ensure that the risk of inadvertent use of a plasmafilter for haemofiltration is minimized.

A list of all the 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 filters intended to perform plasma filtration in humans. If such a filter is used with an extracorporeal circuit, the dimensions of the blood compartment connectors and filtrate compartment connectors 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.

It was not found practicable to specify materials of construction. Therefore, this document only requires that materials used have been tested, and that the testing methods and the 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.

Extracorporeal systems for blood purification —

Part 3:
Plasmafilters

1 Scope

This document specifies requirements and test methods for plasmafilters, which are devices intended to separate plasma from blood in therapeutic plasmapheresis therapy. This document specifies the requirements for sterile, single-use plasmafilters, intended for use on humans, hereinafter collectively referred to as "the device", for use in humans. This document does not apply to;

— extracorporeal blood circuits;

— haemodialysers, haemodiafilters, haemofilters and haemoconcentrators;

— haemoperfusion devices;

— vascular access devices;

— blood pumps;

— systems or equipment intended to perform plasma separation.

NOTE 1 Requirements for the extracorporeal blood circuit are specified in ISO 8637-2.

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

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

ISO 80369-20, *Small-bore connectors for liquids and gases in healthcare applications — Part 20: Common test methods*

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

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 the *plasmafilter* (3.7) through which blood is intended to pass

3.2
blood compartment volume
volume which is needed to fill the *blood compartment* (3.1)

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

3.3
plasma filtrate compartment
part of the *plasmafilter* (3.7) through which filtrate flows

3.4
plasma filtration rate
rate at which plasma is removed from the *blood compartment* (3.1) across the semipermeable membrane into the *plasma filtrate compartment* (3.3) of a *plasmafilter* (3.7)

3.5
labelling
written, printed, graphic or electronic matter that is affixed to the *plasmafilter* (3.7) or any of its containers or wrappers, or that accompanies a plasmafilter, and which is related to the identification, technical description and use of that device, excluding shipping documents

3.6
plasma separation
plasmapheresis
plasma filtration
separation of a portion of the whole plasma from formed elements of blood by means of a semipermeable membrane

Note 1 to entry: Plasma separation can also be accomplished through the use of centrifugation; however, this method is not covered by this document.

3.7
plasmafilter
plasma separator
device intended to perform membrane *plasmapheresis* (3.6)

3.8
sieving coefficient
ratio of a solute concentration in the filtrate to the simultaneous concentration of the same solute on the feed side

3.9
transmembrane pressure
TMP
p_{TM}
mean pressure exerted across the semipermeable membrane contained in the *plasmafilter* (3.7)

Note 1 to entry: The transmembrane pressure is given by Formula (1):

$$p_{TM} = \frac{p_{BI} + p_{BO}}{2} - p_F \quad (1)$$

where

p_{BI} is the pressure at the blood compartment inlet;

p_{BO} is the pressure at the blood compartment outlet;

p_F is the pressure at the filtrate compartment outlet.

4 Requirements

4.1 Biological safety and haemocompatibility

Parts of the plasmafilter 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.

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 and filtrate pathways of the plasmafilter shall be sterile. Compliance shall be verified in accordance with 5.3.

4.3 Non-pyrogenicity

The blood and filtrate pathways of the plasmafilter shall be non-pyrogenic. Compliance shall be verified in accordance with 5.4.

4.4 Mechanical characteristics

4.4.1 Structural integrity

The plasmafilter 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 5.5.1.2 and 5.5.1.3.

4.4.2 Blood compartment integrity

When exposing the blood compartment of the plasmafilter 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 Connectors

4.4.3.1 Plasmafilter blood compartment connectors

Except where the plasmafilter 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.

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

Functional testing shall be performed subject to the manufacturer's risk assessment. Compliance with this requirement shall be verified in accordance with 5.5.3.2.

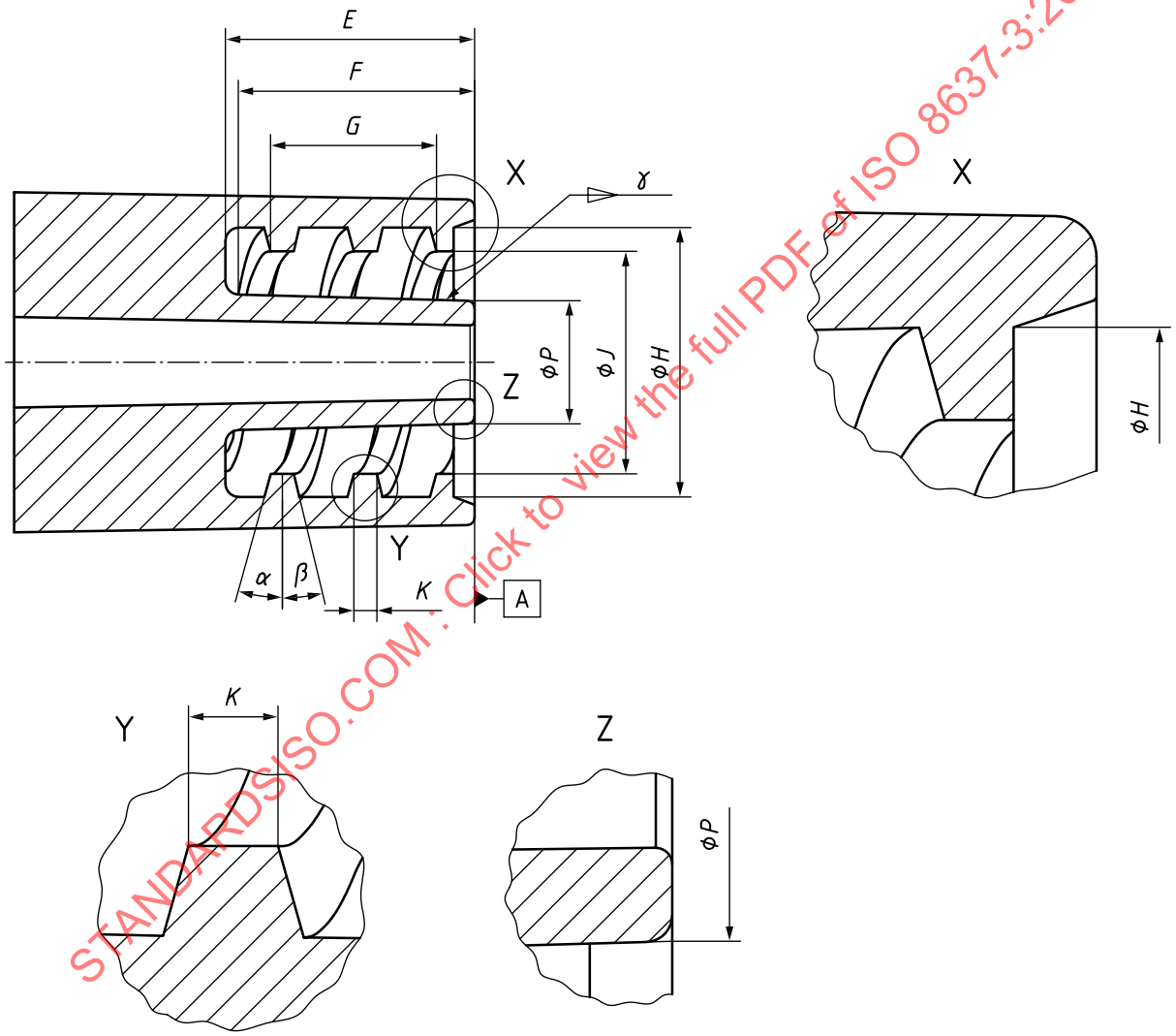


Figure 1 — Cone blood inlet and outlet blood compartment connectors of the plasmafilter

Table 1 — Blood compartment connector dimensions

	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	1,1	6,0	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. Dimension measured as a projection on the front face. See Figure 1 (Z).

4.4.3.2 Plasmafilter filtrate compartment connectors

Except when the plasmafilter and its extracorporeal circuit is designed as an integral system, the plasma filtrate compartment connector shall be as follows:

a) connector design of ISO 8637-1:2023, Figure 2 and Table 2; or

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

c) a non-locking connection for direct attachment of the tubing.

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

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

Functional testing shall be performed subject to the manufacturer's risk assessment.

Compliance with these requirements shall be verified in accordance with 5.5.3.3.

4.5 Performance characteristics

4.5.1 Plasma filtration rate

The plasma filtration rate shall be determined in accordance with 5.6.2. The blood flow rate shall cover the manufacturers specified range for the plasmafilter (see 6.4).

4.5.2 Sieving coefficient

The sieving coefficients for albumin, immunoglobulin G (IgG), immunoglobulin M (IgM), apolipoprotein B (apoB) or low density lipoprotein (LDL), or other equivalent indicators shall be determined in accordance with 5.6.3.

4.5.3 Blood compartment volume

The volume of the blood compartment shall be determined in accordance with 5.6.4.

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.

4.5.4 Blood compartment pressure drop

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

4.5.5 Haemolytic characteristics

The haemolytic characteristics shall be determined in accordance with 5.6.6.

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 or real time aging data. Compliance shall be verified in accordance with 5.7.

5 Test methods

5.1 General

The requirements specified in 4.5 shall be determined prior to marketing a new type of plasmafilter and shall be re-evaluated after changes in the device that can alter its performance.

For the tests, the 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 practicable test apparatus. The design and construction 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, 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 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 plasmafilter 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. Testing shall be carried out in accordance with ISO 10993-1, ISO 10993-4, ISO 10993-7 and ISO 10993-11, as relevant.

5.3 Sterility

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

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

Alternately, a constant negative air pressure at 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 reviewing the validation records of the test procedure.

5.5.3 Connectors

5.5.3.1 General

All connectors for the plasmafilter shall provide a safe connection. To ensure a safe connection, excessive leakage of air from the outside or loss of blood to the environment shall be avoided. The degree of acceptable leakage rate, minimum separation force, minimum separation torque and maximum connection torque at this position in the plasma separation system 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 and ambient temperatures, shall be considered and defined as part of the manufacturer's assessment of the use of the product.

5.5.3.2 Plasmafilter blood compartment connectors

Except when the plasmafilter and the extracorporeal circuit are designed as an integral system, compliance with 4.4.3 shall be determined by dimensional inspection meeting the requirements of Figure 1 and Table 1, and 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 analogue gauge described in Figures 2 to 4 is suitable for determining compliance with the specifications for the cone diameter, *P*, and the dimensional taper rate, *γ*, given in Table 1. Figure 2 and Table 2 indicate the required dimensions and tolerances of the gauge. Figure 3 and Table 3 characterize a socket reference connector for measuring the cone. The gauge of Figure 2 conforms to the dimensions and tolerances of the socket reference connector. Figure 4 illustrates a cone engaged with the gauge meeting the specifications for cone diameter and taper rate of Table 1 and within acceptance window 'a'.

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.

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

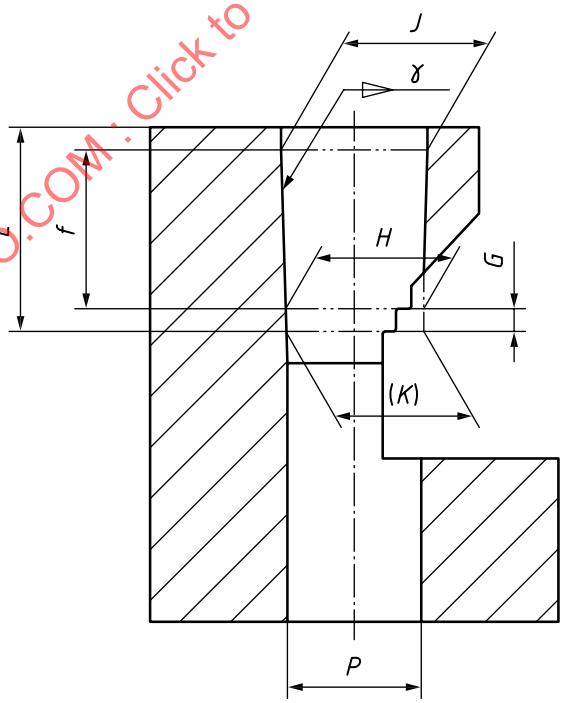


Figure 2 — Socket conical gauge for testing the blood connector cone

Table 2 — Socket conical gauge dimensions

	E [a] mm	f [b] mm	G [c] mm	H mm	J mm	(K) mm	P mm	γ
Minimum	9	—	0,99	6,025	6,444	5,970	—	6:100
Nominal	—	7	1,00	6,030	6,449		—	
Maximum	—	—	1,00	6,030	6,449		5,9	

Key

E length
f length
G length
H cone diameter
J cone diameter
(K) cone diameter
P diameter
γ taper

[a] Reference dimension.
[b] Testing length.
[c] Testing dimension range.

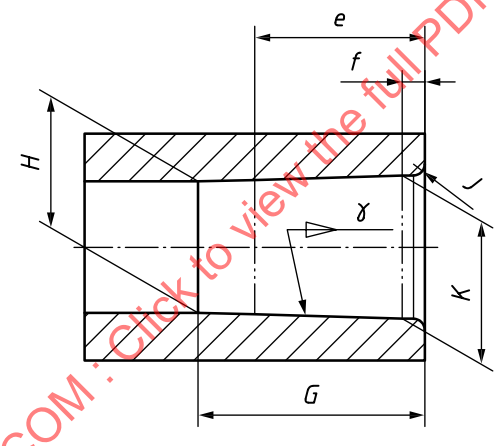


Figure 3 — Socket reference connector for testing the blood connector cone

Table 3 — Socket reference connector dimensions

	e[a] mm	f[b] mm	G[c] mm	H mm	J[b] mm	K[d] mm	γ
Minimum	—	—	10	5,911	—	6,301	
Nominal	7,5	1	—	5,916	—	6,306	6:100
Maximum	—	—	—	5,916	0,5	6,306	

Key

e length

f length

G length

H taper cone

J radius

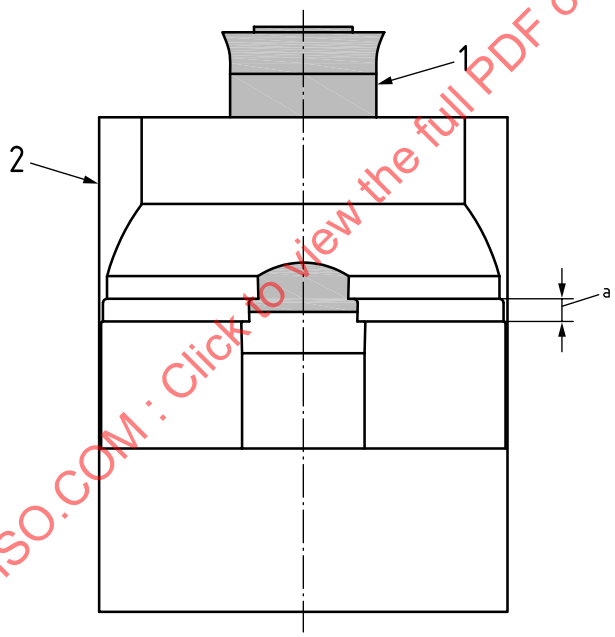
K taper cone

γ taper

[a] Reference dimension for limit of engagement with cone connector.

[b] Reference dimension for the diameter K.

[c] Minimal length of cone.



Key

1 cone

2 gauge

[a] Testing dimensions 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 4 — Illustration of socket conical gauge testing the cone blood connector

5.5.3.3 Plasmafilter plasma filtrate compartment connectors

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.

For connectors having the design of Luer lock connectors of ISO 80369-7:2021, Figures B.1 and B.3, compliance shall be determined by dimensional inspection meeting the requirements of ISO 80369-7.

Non-locking connections shall not separate under an axial force of 25 N applied for 15 s. Locking connections shall comply with 4.4.3 or the test method described in ISO 80369-20.

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.

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.

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

5.6 Performance characteristics

5.6.1 Test solution

The test solution shall be anticoagulated human or bovine blood with a haematocrit value of (32 ± 3) % and a protein concentration of (60 ± 5) g/l.

5.6.2 Plasma filtration rate — Test procedure

Prepare the device consistent with the device's instructions for use to ensure removal of air. Set up the test circuit as shown in Figure 5. Do not allow the pressure during priming to exceed the maximum transmembrane pressure as specified by the manufacturer (see 6.4). Establish stable conditions (temperature, flow and pressure) for blood and plasma filtrate flows and ensure all air is removed from the plasmafilter. Perform plasma filtration rate measurements under the stable conditions at a range of blood flow rates which include the minimum and maximum blood flow rates specified by the manufacturer.

NOTE The relationship between plasma filtration rate and transmembrane pressure (TMP) can deviate from linearity and attain a maximum value which can remain constant despite an increasing transmembrane pressure. This plateau represents the maximum filtration flow rate for the device.

5.6.3 Sieving coefficient

5.6.3.1 Test solution

The test solution shall be anticoagulated human or bovine plasma with a protein concentration of (60 ± 5) g/l and contain one or more of the following substances or equivalent indicators:

— albumin (present as plasma albumin);

— IgG;

— apoB or LDL;

— IgM.

NOTE Alternate substances or whole blood can also be used.

5.6.3.2 Test procedure

Set up the test circuit with either a recirculating fluid configuration [see Figure 5 a)] or single pass fluid configuration [see Figure 5 b)] to assess the sieving coefficient. Prior to testing, devices shall be prepared in accordance with their instructions for use as typically used for treatments and all air shall be removed from the circuit. The temperature of the test solution shall be maintained at (37 ±1) °C throughout the experiment using a heat exchanger. Priming fluid shall be discarded in a way that total protein concentration of the

plasma stays in the range of (60 ± 5) g/l. Flow rates shall be kept constant throughout the experiment and stability of pressure, temperature and flow rates shall be verified. Set the test solution flow rate to the maximum blood flow rate stated by the manufacturer (see 6.4) and adjust the plasma filtration rate to at least 20 % of the test solution flow rate. If for device-related reasons the stated test solution flow rate cannot be achieved, use the maximum possible flow rate and record the rate used.

Collect test samples after steady-state has been reached (typically after 30 min of blood contact) from the blood inlet and filtrate sides and measure albumin, IgG, apoB or LDL, and IgM concentrations.

5.6.3.3 Calculation of the sieving coefficient

The sieving coefficient, S, can be calculated using Formula (2):

$$S = \frac{c_F}{c_{BI}} \quad (2)$$

where

S is the sieving coefficient;

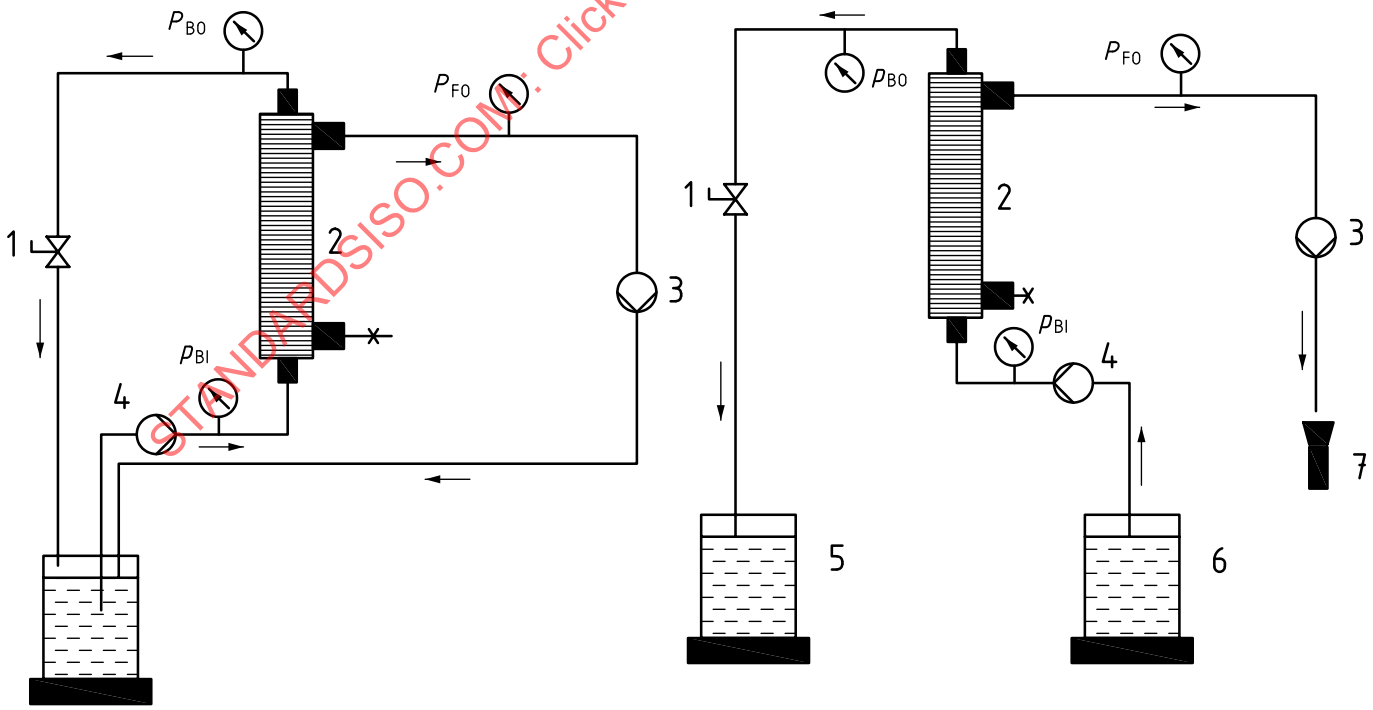
c_{BI} is the concentration of the solute at the blood inlet side of the plasmafilter;

c_F is the concentration of the solute at the filtrate side of the plasmafilter.

NOTE 1 In Formula (2), it is necessary to use the same units of concentration for C_{Bi} and C_F.

To assess the impact of membrane fouling on sieving coefficient the measurements, repeat the measurements at a second time point (typically after 90 min of blood contact).

NOTE 2 Although Figures 5 a) and b) show the blood entering the plasmafilter at the bottom, the test procedure can also be performed with the blood entering the top, and/or the plasmafilter in a horizontal position, provided these configurations have been shown to produce equivalent results to those obtained with the plasmafilter in the vertical position and with blood entering at the bottom.



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

Key

1	pressure control	6	test solution reservoir
2	plasmafilter	7	waste
3	filtrate pump	p_{BO}	blood compartment pressure, out
4	blood pump	p_{BI}	blood compartment pressure, in
5	test solution reservoir	P_{FO}	filtrate pressure, out

Figure 5 — Diagram of systems for the measurement of the ultrafiltration and sieving coefficient

5.6.4 Blood compartment volume

The blood compartment volume shall be calculated from geometrical data (volume of the header compartments, fibre dimensions and number of fibres). Compliance is checked by inspection of the manufacturer's documentation.

NOTE The volume of the blood compartment is calculated as described above since it can prove difficult to find a liquid that will not be filtered through the plasmafilter membrane.

5.6.5 Blood compartment pressure drop

5.6.5.1 General

Compliance with 4.5.4 shall be determined in accordance with the test described in 5.6.4.

5.6.5.2 Test solution

A test solution of anticoagulated bovine or human blood, with a haematocrit of (32 ± 3) % and a protein concentration of (60 ± 5) g/l, shall be used to establish the pressure drop in the blood pathway.

5.6.5.3 Test procedure

Establish the blood flow rate at which the measurement will be performed. Run in a single pass configuration until the plasma filtrate compartment is full and cap both ends of the compartment. Switch the flow configuration to the recirculation mode, establish the blood flow rate, record the inlet and outlet pressures to the blood compartment, and repeat over the manufacturers' stated range of flow rates.

Compliance is checked by inspection of the manufacturer's documentation (see 6.4).

5.6.6 Haemolytic characteristics

5.6.6.1 General

Haemolysis is the rupturing (lysis) of red blood cells (erythrocytes) and the release of their contents (cytoplasm) into surrounding fluid (e.g. blood plasma) and can occur during plasma separation from shear stress. It is characterized by the presence of free haemoglobin (fHb) in the plasma which changes colour from yellow to pink. In the case of excessive fHb, the colour of the plasma becomes dark red.

5.6.6.2 Test solution

A test solution of anticoagulated bovine or human blood, with a haematocrit of (32 ± 3) % and a protein concentration of (60 ± 5) g/l shall be used to establish the haemolytic characteristics of the device.

5.6.6.3 Test procedure

Set up a test circuit as shown in Figure 5. Take a sample from the test solution, and set the blood flow at the minimum rate and the transmembrane pressure at the maximum value as specified by the manufacturer.

Allow the test solution to flow through the plasmafilter under test for 30 min ensuring that the set conditions are maintained.

During this period, sample the filtrate that is being produced. Quantification of the amount of free plasma haemoglobin present can be made by its measurement over the study period by sampling at the beginning and end of the period. The free plasma haemoglobin can be measured by using a spectrophotometric or colorimetric assay. Alternate measurement methods are acceptable, provided such methods have been appropriately validated.

The observed haemolysis rate derived from the level of free plasma haemoglobin shall be specified.

NOTE The value of the free haemoglobin in the plasma will be a function of not only the damage that is induced by the plasmafilter, but also that arising from the blood pump. To quantify the blood pump induced damage, free haemoglobin is measured by circulating only in the circuit without the plasmafilter.

5.6.6.4 Expression of haemolysis rate

The observed haemolysis rate can be expressed either in terms of plasma free haemoglobin level (mg/dl) or in terms of the normalized index of haemolysis (NIH) where NIH is given by Formula (3):

$$\Delta c_{\mathrm{FHb}} \cdot V\left[\frac{100-x_{\mathrm{Hct}}}{100}\right] \cdot \frac{100}{q \cdot T} \tag{3}$$

where

Δc_{FHb} is the increase of plasma free haemoglobin concentration over the sampling time interval, in g/l;

V is the circulating blood volume, in l;

q is the flow rate, in l/min;

x_{Hct} is the haematocrit, in %;

T is the sampling time interval, in min.

5.7 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.

6 Labelling

6.1 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 (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;