INTERNATIONAL STANDARD

**ISO 8637-3**

First edition
2018-07

# 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 documents 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).

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. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

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

For an explanation on 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 the following URL: 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 first edition of ISO 8637-3:2018 cancels and replaces the second edition of ISO 13960:2010, which has been technically revised. The following changes have been made:

— the Figures relating to connector dimensions have been revised.

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



# Introduction

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.

If the plasmafilter 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.

This document reflects the consensus of physicians, manufacturers and other interested parties for devices that are approved for clinical use.

# Extracorporeal systems for blood purification —

# Part 3:
# Plasmafilters

## 1 Scope

This document specifies requirements and acceptance criteria (including test methods) for safety related parameters for plasmafilters. Only those requirements that are specific to plasmafilters have been included.

It specifies requirements for sterile, single-use plasmafilters, intended for use on humans.

This document does not cover matters related to toxicity. Such issues are covered in relevant parts of ISO 10993.

It does not apply to the extracorporeal circuits that can be used for plasmapheresis vascular access devices, oxygenators or active medical devices. This document does not address the replacement fluid.

## 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 8637-1, *Extracorporeal systems for blood purification — Part 1: Haemodialysers, haemodiafilters, haemofilters and haemoconcentrators*

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 80369-7, *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 terminological databases for use in standardization at the following addresses:

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

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

**3.1**
**blood compartment**
part of plasmafilter through which blood is intended to pass

**3.2**
**filtrate compartment**
part of plasmafilter through which filtrate flows

**3.3**
**filtration rate**
rate at which fluid is removed from the *blood compartment* (3.1) across the semipermeable membrane into the *filtrate compartment* (3.2) of a plasmafilter

**3.4**
**plasmapheresis**
**plasma separation**
separation of a portion of the whole plasma from formed elements of blood by means of a semipermeable membrane

Note 1 to entry: Plasmapheresis can also be accomplished through the use of differential centrifugation but this method is not covered by this document.

**3.5**
**plasmafilter**
device intended to perform membrane *plasmapheresis* (3.4)

**3.6**
**sieving coefficient**
ratio of a solute concentration in the filtrate to the simultaneous concentration of the same solute in blood

**3.7**
**transmembrane pressure**
**TMP**
$p_{TM}$
mean pressure exerted across the semipermeable membrane

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 blood compartment inlet;

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

$p_F$ is the pressure at filtrate compartment outlet.



# 4 Requirements

## 4.1 Biological safety

Parts of the device that will come into direct or indirect contact with blood during their intended clinical use shall be biocompatible with respect to their intended clinical use.

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.

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.

Conformity shall be verified in accordance with 5.2.

## 4.2 Sterility

The blood and filtrate pathways of the device shall be sterile. Conformity shall be verified in accordance with 5.3.

## 4.3 Non-pyrogenicity

The blood and filtrate pathways of the device shall be non-pyrogenic. Conformity 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, plasmafilters shall not leak.

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

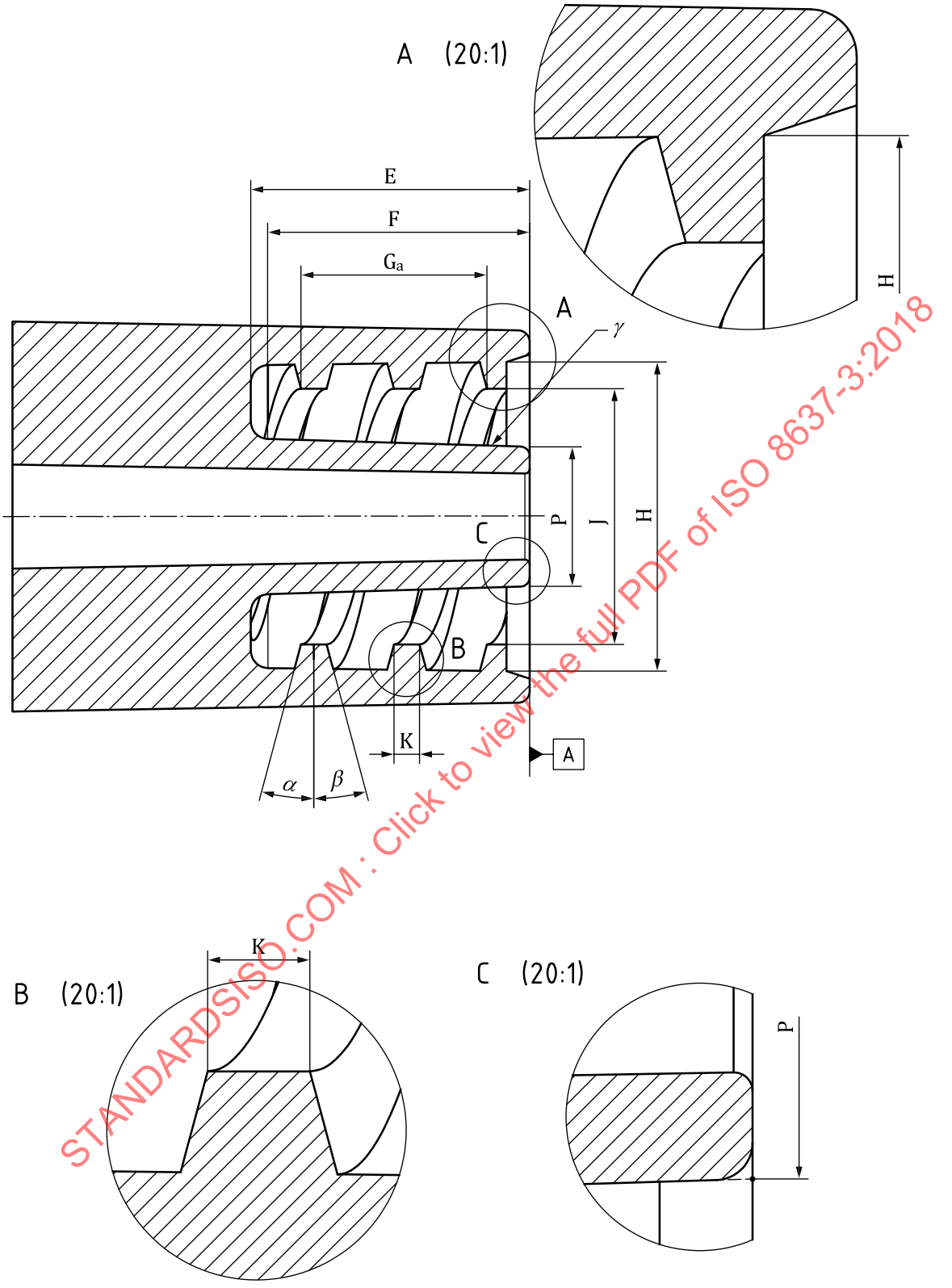
### 4.4.2 Blood compartment integrity

When tested in accordance with 5.5.2, the blood compartment shall not leak.

### 4.4.3 Connectors and ports

#### 4.4.3.1 Blood Compartment Ports

Except where the plasmafilter and the extracorporeal blood circuit are designed as an integral system, the dimensions of the blood ports shall be as given in Figure 1. Conformity to this requirement shall be verified in accordance with 5.5.3.






**Key**

| Symbol | Designation | Dimension in mm | Comments |
|---|---|---|---|
| $\alpha$ | Angle of thread | 15° | — |
| $\beta$ | Angle of thread | 15° | — |
| $\gamma$ | Dimension taper rate | 6:100 | — |
| E | Length of thread | 10 or more | — |

| Symbol | Designation | Dimension in mm | Comments |
|---|---|---|---|
| F | Length of tapered region | 9 or more | — |
| G[a] | Thread pitch | 8 | The superscript "a" of G[a] means double thread. |
| H | Root diameter | 13 or more | — |
| J | Crest diameter | 11<br>+0,3<br>-0,2 | Altered upper tolerance to accommodate different components and materials. |
| K | Thread crest width | 1,1<br>±0,25 | Revised dimension and tolerances based on existing manufacturing practice. |
| P | cone diameter male<br>plane of reference"A square" | 6<br>±0,03 | This dimension to be measured as a projection on the front face. See Figure 1 (C). |

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

#### 4.4.3.2 Connection to the plasma filtrate compartment

The filtrate ports of plasmafilters shall allow for a secure connection to the tubing which is to be used with the device, except when plasmafilters and their extracorporeal circuits are designed as an integral system.

The dimensions of the filtrate ports shall be a male 6% (Luer) taper lock fitting in accordance with ISO 80369-7 or dialysis fluid inlet and outlet ports in accordance with ISO 8637-1.

Conformity to this requirement shall be verified in accordance with 5.6.

Connectors made of semi-rigid materials shall not separate under an axial force of 15 N for 15 s.

### 4.4.4 Volume of the blood compartment

When measured in accordance with 5.5.4, the volume of the blood compartment of the plasmafilters shall be within the range of values stated by the manufacturer [see 6.2 h)].

### 4.4.5 Pressure drop of the blood compartment

When measured in accordance with 5.7.2, the pressure drop across the blood compartment of the plasma filter shall be within the range of values stated by the manufacturer [see 6.2 h)].

## 4.5 Performance characteristics

### 4.5.1 Filtration rate

When measured in accordance with 5.8.1.2, the filtration rate shall be within the range of values stated by the manufacturer [see 6.4 i)].

### 4.5.2 Sieving coefficient

When measured in accordance with 5.8.2.2, the sieving coefficients for albumin, immunoglobulin M (IgM) and beta lipoprotein or equivalent indicators shall be within the range of values stated by the manufacturer [see 6.4 i)].

#### 4.5.3 Haemolytic characteristics

The device shall not cause haemolysis that represents a safety hazard to patients when tested at the maximal operating conditions. Testing shall be in accordance with 5.8.3.2.

### 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. Conformity shall be in accordance with 5.9.

## 5 Test methods

### 5.1 General

The performance characteristics specified in 4.3 shall be determined prior to marketing a new type of device and shall be re-evaluated after changes in the device that might alter its performance.

The sample of device shall be drawn at random from the manufacturer's production and shall have passed all applicable quality control steps, as well as sterilization. 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 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 and the establishment of actual test systems shall also address the many factors contributing to measurement error, including, but not limited to, pressure measurement errors due to static head effects and dynamic pressure drops; parameter stabilization time; uncontrolled temperature variations at the non-constant flow rates; pH; degradation of test substances due to heat, light and time; degassing of test fluids; trapped air and system contamination by foreign material, algae and bacteria.

The test methods below are reference methods. Other methods may be used, provided they have been shown to be of comparable precision and reproducibility.

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 (see 5.8).

Others are of a quality control nature, which are repeated on a regular basis to ensure that the device fulfils requirements (see 5.2, 5.3, 5.4, 5.5.1, 5.5.2).

### 5.2 Biological safety

The biological safety of plasmafilters 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 or ISO 10993-11, as relevant.

### 5.3 Sterility

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

### 5.4 Non-pyrogenicity

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



## 5.5 Mechanical characteristics

### 5.5.1 Structural integrity

The device shall be capable of withstanding a positive pressure of 1,5 times the manufacturer's recommended maximum pressure above atmospheric pressure and a negative pressure not exceeding 700 mmHg (93,3 kPa below atmospheric pressure) or the highest obtainable negative pressure if at high elevation, when tested according to 5.5.2.

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

Fill the device under test with water and subject the device to a 1,5 times the manufacturers recommended maximum pressure. Maintain this pressure for 10 min and visually inspect the device for any emergence of water.

### 5.5.2 Blood compartment integrity

Set up the filter in the vertical position. Close off the bottom filtrate and blood ports. Wet the membrane with water and fill the filtrate compartment, if appropriate. Pressurize the blood compartment with air to 1,5 times the maximum transmembrane pressure specified by the manufacturer for a period of 10 min. If no bubbles exit the filtrate compartment, through the open filtrate port, the blood compartment is intact.

### 5.5.3 Blood compartment ports

Conformity to 4.4.3.1 shall be determined by inspection. If a non locking connector is used, the connector shall not separate under an axial force of 15 N applied for 15 s.

### 5.5.4 Blood compartment volume

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

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

## 5.6 Plasma filtrate port

Conformity to 4.4.3.2 shall be determined by visual inspection.

## 5.7 Pressure drop

### 5.7.1 Test solution

The test liquid shall be anticoagulated bovine or human blood, with a haematocrit value of (32 ± 3) % and protein content of (60 ± 5) g/l and sustained during the test procedure.

### 5.7.2 Pressure drop test procedure

Fill the filtrate compartment with saline or plasma and the blood compartment with the test fluid. Measure the pressure drop across the blood compartment over the manufacturer's stated range of blood flow rates.

## 5.8 Performance characteristics

### 5.8.1 Filtration rate

#### 5.8.1.1 Test solution

The test liquid shall be anticoagulated bovine or human blood, with a haematocrit value of (32 ± 3) % and protein content of (60 ± 5) g/l and sustained during the test procedure.

#### 5.8.1.2 Filtration rate test procedure

Set up a test circuit as shown in Figure 2. Do not allow the priming pressure to exceed the maximum transmembrane pressure stated by the manufacturer [see 6.1 h)]. Make measurements of plasma flow rates with the test liquid circulating through the blood compartment of the device under test and in sequence of measurement from minimum to maximum transmembrane pressure at each blood flow rate stated by the manufacturer [see 6.4 d) 1)].

### 5.8.2 Sieving coefficient

#### 5.8.2.1 Test solution

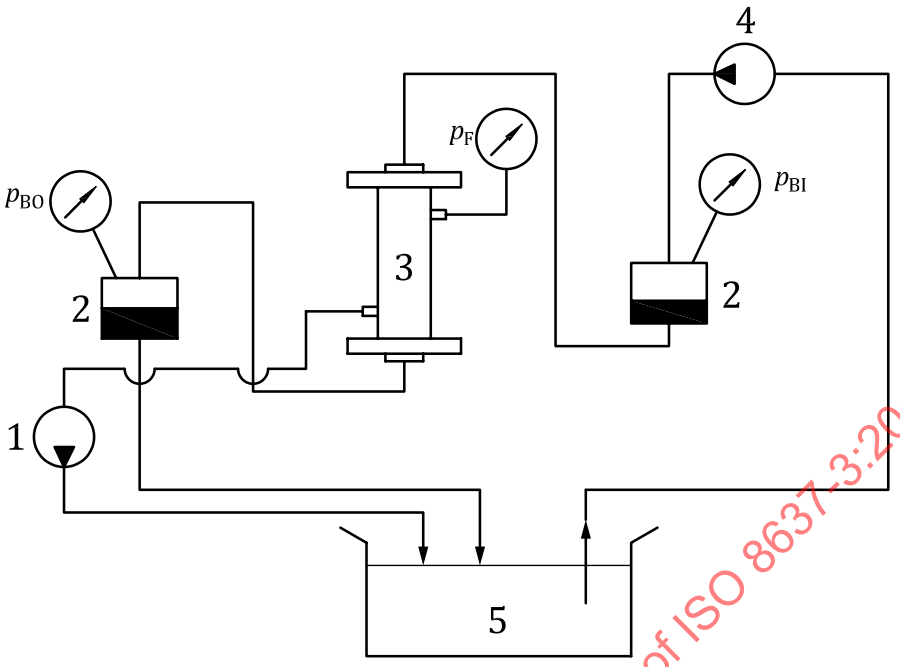
The test liquid shall be bovine or human plasma with a protein content of (60 ± 5) g/l and containing one or more of the following substances or equivalent indicators:

a) albumin (present as plasma albumin);

b) immunoglobulin M (IgM);

c) $\beta$-lipoprotein.

NOTE Further substances/indicators or whole blood can be used.




**Key**

| | |
|---|---|
| 1 | plasma pump |
| 2 | chamber |
| 3 | device under test |
| 4 | blood pump |
| 5 | test liquid at (37 ± 1) °C |
| $p_{BI}$ | is the pressure of blood at the inlet of the device under test |
| $p_{BO}$ | is the pressure of blood at the outlet of the device under test |
| $p_F$ | is the pressure of the filtrate at the outlet of the device under test |

**Figure 2 — Schematic test circuit for determination of the filtration rate and sieving coefficient**

#### 5.8.2.2 Sieving coefficient test procedure

Set up a test circuit as shown in Figure 2.

Establish stable conditions (temperature, flow and pressure) and ensure that all air has been removed from the blood pathway. Measure the protein content of the test liquid and record this value. Set the test liquid flow rate to the maximum blood flow rate stated by the manufacturer [see 6.4 d) 2)] and the filtration rate to at least 20 % of the test liquid flow rate. If, for device related reasons, the stated test liquid flow rate cannot be achieved, use the maximum possible rate and record the rate used.

Collect test samples after steady-state has been reached (typically after 30 min of blood contact). Measure the concentration of the protein in the filtrate. The measurements should be repeated at a second time point (typically after 90 min of blood contact) to evaluate membrane fouling.

Calculate the sieving coefficient, $S$, using Formula (2):

$$S = \frac{c_F}{c_{BI}} \tag{2}$$

where

$c_F$ is the concentration of a solute in the filtrate;

$c_{BI}$ is the concentration of a solute at the inlet of the device under test.

#### 5.8.3 Haemolytic characteristics

##### 5.8.3.1 Test solution

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

##### 5.8.3.2 Haemolytic characteristics test procedure

Circulate the test liquid for 30 min using the maximum transmembrane pressure and the minimum blood flow rate specified by the manufacturer.

During this period, visually inspect the filtrate for the presence of blood. Measure free haemoglobin in the blood and filtrate at the beginning and end of the procedure. The change in level should be within the manufacturer's specifications.

NOTE The conditions stated above represent the maximal conditions under which the device is operated.

### 5.9 Expiry date

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

## 6 Labelling

### 6.1 Labelling on the device

The device 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 the filtrate 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;

j) a warning that the device is intended only for use in plasma separation.

Where symbols exist as shown in ISO 7000 and/or ISO 15223-1 these may be used as an alternative.



## 6.2 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 manufacturers 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;

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

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

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

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

Instructions for use should include the statement or symbol “Do not use the device if package is damaged.” If protective end caps are used for sterile production, then the statement “Do not use the device if the protective end caps are not in place”.

j) a statement that the device shall be used with a machine indicated for plasma filtration.

Where symbols exist as shown in ISO 7000 and/or ISO 15223-1 these may be used as an alternative.

## 6.3 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 and in accordance with national requirements;

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 or if protective end caps are not in place”.

Where symbols exist as shown in ISO 7000 and/or ISO 15223-1 these may be used as an alternative.