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Haemodialysers, haemofilters and haemoconcentrators

Hémodialyseurs, hémofiltres et hémoconcentrateurs

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Contents

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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.

Draft International Standards adopted by the technical committees are circulated to the member bodies for approval before their acceptance as International Standards by the ISO Council. They are approved in accordance with ISO procedures requiring at least 75 % approval by the member bodies voting.

International Standard ISO 8637 was prepared by Technical Committee ISO/TC 150, *Implants for surgery*.

Annex A forms an integral part of this International Standard.

Introduction

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

It was not found practicable to specify materials of construction nor to give test methods for biocompatibility, validation of sterility, non-pyrogenicity and some performance characteristics of the device. This International Standard therefore requires only that materials will have been tested and that the methods and results are made available upon request. There is no intention to specify, or to set limits on, the performance characteristics of the devices because such restrictions are unnecessary for the qualified user and would limit the alternatives available when choosing a device for a specific application.

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

Attention is drawn to the work of Sub-committee 62D, *Electromedical equipment*, of the International Electrotechnical Commission (IEC) regarding the electrotechnical aspects of dialysis systems. There is no IEC publication dealing with haemofiltration or haemoconcentration systems.

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

Haemodialysers, haemofilters and haemoconcentrators

1 Scope

This International Standard specifies requirements for haemodialysers, including those of coil, hollow fibre and parallel plate design, haemofilters and haemoconcentrators for single use for humans.

Materials of construction and test methods for biocompatibility, validation of sterility, non-pyrogenicity and some performance characteristics are not specified; the rationale for these omissions is given in the Introduction.

This International Standard does not apply to devices assembled and sterilized by the user; the extracorporeal blood circuit, plasma filters, haemoperfusion devices, vascular access devices, blood pumps, pressure monitors of the extracorporeal circuit, air detection devices or systems to prepare, maintain or monitor dialysing fluid.

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

2 Normative references

The following standards contain provisions which, through reference in this text, constitute provisions of this International Standard. At the time of publication, the editions indicated were valid. All standards are subject to revision, and parties to agreements based on this International Standard are encouraged to investigate the possibility of applying the most recent editions of the standards listed below. Members of IEC and ISO maintain registers of currently valid International Standards.

ISO 472 : 1979, *Plastics — Vocabulary.*

ISO 8638 : 1989, *Extracorporeal blood circuit for haemodialysers, haemofilters and haemoconcentrators.*

3 Definitions

For the purposes of this International Standard, the following definitions apply.

3.1 arterial blood circuit: Portion of the extracorporeal blood pathway from the vascular access device of the patient to the blood inlet of the haemodialyser, haemofilter or haemoconcentrator.

3.2 blood compartment volume; volume of the blood compartment: Volume of blood required to fill the haemodialyser, haemofilter or haemoconcentrator at a given transmembrane or mean coil pressure.

3.3 blood flow rate, q_{V_B}: Quantity of blood flowing through the haemodialyser, haemofilter or haemoconcentrator per unit time.

NOTE — The blood flow rate is usually expressed in millilitres per minute.

3.4 clearance, q_{V_C}: Net flux of solute across the haemodialyser or haemofilter, calculated using the following equations, as appropriate:

For haemodialysis, using an open loop

$$q_{V_C} = \left(\frac{c_A - c_V}{c_A} q_{V_B} \right) + \left(\frac{c_V}{c_A} q_{V_F} \right) \quad \ldots (1)$$

NOTE — $\frac{c_V}{c_A} q_{V_F}$ represents the clearance due to convection.

For haemodialysis, using a closed loop

$$q_{V_C} = q_{V_F} \left[\frac{b \, \Delta t}{\ln \left(1 - \frac{q_{V_F} \Delta t}{V_0} \right)} + 1 \right] \quad \ldots (2)$$

NOTE — It has been found that q_{V_F} has to be greater than 2 ml/min to achieve accurate results.

For haemofiltration

$$q_{V_C} = \frac{q_{V_F} \times c_F}{c_A} \quad \ldots (3)$$

In equations (1) and (3), it is necessary to use the same units of measurement for c_A, c_V and c_F.

In equations (1) to (3)

b is the slope of linear regression of the natural logarithm of the reservoir concentration over time;

c_A is the concentration of solute on the inlet side of the haemodialyser or haemofilter;

c_F is the filtrate concentration;

c_V is the concentration of solute on the outlet side of the haemodialyser or haemofilter;

q_{V_B} is the blood flow rate, in millilitres per minute, at the inlet of the device;

q_{V_F} is the filtrate flow rate (ultrafiltration rate), in millilitres per minute;

Δt is the duration of the test, in minutes ($t - t_0$), where t_0 is the time at the beginning of the test and t the time at the end of the test;

V_0 is the volume of the "blood" reservoir, in millilitres, at time t_0.

NOTES

1 The term "ultrafiltration" is commonly used as a synonym for "filtration" in haemodialysis.

2 Clearance is usually expressed as the number of millilitres of blood completely cleared of the solute per minute (corrected for ultrafiltration).

3.5 clotted residual blood: Residual blood that cannot be recovered by rinsing the blood compartment.

3.6 compliance: Change in volume of the blood compartment of the haemodialyser, haemofilter or haemoconcentrator in relation to change in transmembrane pressure.

NOTE — Compliance is usually expressed in millilitres per 100 millimetres of mercury of transmembrane pressure or mean coil pressure.

3.7 dialysance, q_{V_D}: Rate of exchange per unit time of a solute between blood and dialysing fluid per unit blood to dialysing fluid concentration gradient, calculated using the following equation:

$$q_{V_D} = \left(\frac{c_A - c_V}{c_A - c_D} q_{V_B} \right) + \left(\frac{c_V}{c_A - c_D} q_{V_F} \right) \quad \ldots (4)$$

where

c_D is the concentration of the solute entering the haemodialyser;

the other symbols are as defined in 3.4.

It is necessary to use the same units of measurement for c_A, c_V and c_D.

NOTES

1 Clearance may be derived from dialysance for recirculating dialysing fluid systems using the following equation:

$$q_{V_C} = \frac{q_{V_D}}{1 + \frac{q_{V_D}}{q_{V_d}}} \quad \ldots (5)$$

where q_{V_d} is the dialysing fluid flow rate.

2 Dialysance measurement is useful for comparing devices in systems where the concentration of the solute in the dialysing fluid entering the haemodialyser is greater than zero, e.g. in recirculation single-pass systems.

3 Dialysance is equal to the clearance in single-pass systems, i.e. when $c_D = 0$.

3.8 dialysate; dialysing fluid: Solution used to perfuse a compartment that is separated from the blood in a haemodialyser by the semi-permeable membrane.

3.9 dialysing fluid compartment volume; volume of the dialysing fluid compartment: Volume of the dialysing fluid required to fill the dialysing fluid compartment of the haemodialyser at a given transmembrane pressure.

3.10 dialysing fluid addition rate: Rate at which fresh dialysing fluid is added to a recirculation single-pass system.

NOTE — The dialysing fluid addition rate is usually expressed in millilitres per minute.

3.11 dialysing fluid flow rate, q_{V_d}: Rate at which dialysing fluid enters the haemodialyser.

NOTE — The dialysing fluid flow rate is usually expressed in millilitres per minute.

3.12 dialysing fluid recirculation rate: In coil haemodialysers, the rate at which dialysing fluid is recirculated through the device.

NOTE — The dialysing fluid recirculation rate is usually expressed in millilitres per minute.

3.13 distributor: Any party other than the manufacturer who offers the haemodialyser, haemofilter or haemoconcentrator for sale.

3.14 filtrate: Fluid removed from the blood compartment across the semi-permeable membrane into the dialysate or filtrate compartment of a haemodialyser, haemofilter or haemoconcentrator due to a pressure gradient across the semi-permeable membrane.

3.15 fluid residual blood: Residual blood that can be recovered by further rinsing of the blood compartment after rinsing as recommended by the manufacturer.

3.16 haemoconcentration: Treatment whereby extracorporeal blood is passed through a device (the haemoconcentrator) for the sole purpose of removing fluid from the blood.

NOTE — In haemoconcentration, blood flows through one part of a chamber divided by a semi-permeable membrane. The filtrate passing through the membrane is collected in the other part of the chamber and is led to waste. The permeability of the membrane does not allow clinically significant loss of protein from the blood.

3.17 haemoconcentrator: Device used to perform haemoconcentration.

3.18 haemodialyser: Device used to perform haemodialysis.

3.19 haemodialysis: Treatment whereby extracorporeal blood is passed through a device (the haemodialyser) that allows the transfer of substances by diffusion and convection for the purpose of decreasing biochemical abnormalities as well as fluid, electrolyte and acid-base imbalances.

NOTE — In haemodialysis, the blood flows through a chamber divided by a semi-permeable membrane, on the other side of which flows the dialysing fluid. Solute exchange between the blood and the dialysing fluid is mainly due to diffusion. Fluid exchange between the blood and dialysing fluid is mainly due to ultrafiltration. The permeability of the membrane does not allow clinically significant loss of protein from the blood.

3.20 haemofilter: Device used to perform haemofiltration.

3.21 haemofiltration: Treatment whereby extracorporeal blood is passed through a filtration device (the haemofilter) for the purpose of decreasing biochemical abnormalities as well as fluid, electrolyte and acid-base imbalances, which is achieved by the exchange of a filtrate of the blood for an appropriate volume of a physiological replacement solution.

NOTE — In haemofiltration, the blood flows through a chamber divided by a semi-permeable membrane on the other side of which flows a physiological replacement solution which infuses into the bloodstream. The permeability of the membrane does not allow clinically significant loss of protein from the blood.

3.22 hydraulic resistance: Blood or dialysing fluid compartment flow resistance measured as the pressure drop, in millimetres of mercury, or change in pressure, p, between inlet and outlet ports of the haemodialyser, haemofilter or haemoconcentrator at a given flow rate.

3.23 manufacturer: Party that assumes responsibility for quality assurance of the final product.

3.24 mean coil pressure (MCP), p_{MC}: Arithmetic mean of the inlet and outlet pressure of the blood pathway of a coil haemodialyser with an open dialysing fluid compartment, calculated using the following equation:

$$p_{MC} = \frac{p_{B,i} + p_{B,o}}{2} \quad \ldots (6)$$

where

$p_{B,i}$ is the pressure of blood on the arterial side of the haemodialyser, in millimetres of mercury;

$p_{B,o}$ is the pressure of blood on the venous side of the haemodialyser, in millimetres of mercury.

3.25 non-pyrogenic: Free of pyrogenic material within the limit of error of test methods for such determinations, as defined by the national regulatory agency of the country in which the device is to be marketed or, where available, an International Standard, and maintained in that state by suitable protection.

3.26 recirculation system: Dialysing fluid system in which the dialysing fluid is recirculated through the haemodialyser repeatedly during dialysis.

3.27 recirculation single-pass system: Dialysing fluid system in which the dialysing fluid is recirculated repeatedly through the haemodialyser during dialysis and the recirculating volume is displaced continuously to waste by fresh dialysing fluid.

3.28 residual blood: Volume of blood remaining in the haemodialyser, haemofilter or haemoconcentrator after the procedure recommended by the manufacturer for returning the blood from the device to the patient.

NOTE — Residual blood is usually expressed in millilitres.

3.29 semi-permeable membrane: Membrane used to separate blood from dialysing fluid in haemodialysis or through which filtrate passes in haemofiltration or haemoconcentration.

3.30 single-pass dialysing fluid system: Dialysing fluid system in which the dialysing fluid flows to waste after one passage through the haemodialyser.

3.31 sterile: Free from all living organisms within the limits of validation tests for sterility and maintained in that state by suitable protection.

3.32 transmembrane pressure (TMP), p_{TM}: Hydrostatic pressure exerted across the semi-permeable membrane of certain haemodialysers (hollow-fibre, parallel-plate, coil with closed dialysate compartment) or a haemofilter, calculated using the following equations:

For haemodialysis

$$p_{TM} = \frac{p_{B,i} + p_{B,o}}{2} - \frac{p_{d,i} + p_{d,o}}{2} \quad \ldots (7)$$

For haemofiltration

$$p_{TM} = \frac{p_{B,i} + p_{B,o}}{2} - p_F \quad \ldots (8)$$

where

$p_{d,i}$ is the pressure of dialysing fluid on the inlet side of the haemodialyser;

$p_{d,o}$ is the pressure of dialysing fluid on the outlet side of the haemodialyser;

p_F is the pressure at the outlet of the filtrate compartment;

$p_{B,i}$ and $p_{B,o}$ are as defined in 3.24.

3.33 user: Operator of a device.

3.34 venous blood circuit: Extracorporeal blood circuit from the outlet of the haemodialyser, haemofilter or haemoconcentrator, returning blood to the vascular access device of the patient.

4 Requirements

4.1 Good manufacturing practice

The haemodialyser, haemofilter or haemoconcentrator shall be manufactured in a clean environment and the fluid pathways shall be free of visible foreign material.

NOTE — Attention is drawn to the need to establish whether codes for good manufacturing practice exist in the country in which the device is produced and, if applicable, in the countries in which the device is to be marketed.

Testing shall be carried out in accordance with 5.1.

4.2 Toxicology and biological compatibility

Samples of the device shall be tested for freedom from toxicity using, if available, the method specified in the relevant national standard and the results of such tests shall indicate freedom from biological hazard. If requested, details of the test method and the results shall be made available by the manufacturer of the device.

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

Testing shall be carried out in accordance with 5.2.

4.3 Sterility

The fluid pathways of the device shall be supplied sterile.

NOTE — Attention is drawn to the need to establish whether national regulations or national standards governing sterility 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.

Testing shall be carried out in accordance with 5.3.

4.4 Pyrogenicity

The blood pathway(s) of the device shall be non-pyrogenic. If requested, details of the test method(s) and the results shall be made available by the manufacturer of the device.

NOTE — Attention is drawn to the need to establish whether national regulations or national standards governing pyrogen 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.

Testing shall be carried out in accordance with 5.4.

4.5 Residues from sterilization

After sterilization by the procedure recommended by the manufacturer, the device shall be tested for freedom from toxic residues that have adverse chemical, physical or biological effects on the blood or that result in release of clinically significant amounts of potentially toxic substances into the blood. If requested, details of the test methods and the results shall be made available by the manufacturer of the device.

NOTE — Attention is drawn to the need to establish whether national regulations or national standards governing testing for residues from sterilization exist in the country in which the device is produced and, if applicable, in the countries in which the device is to be marketed.

Testing shall be carried out in accordance with 5.5.

4.6 Mechanical characteristics

4.6.1 Structural integrity

Samples of the haemodialyser, haemofilter or haemoconcentrator shall be capable of withstanding 1,5 times the maximum transmembrane pressure or mean coil pressure specified by the manufacturer. Devices with a closed dialysing fluid compartment or filtrate compartment shall also withstand a subatmospheric pressure that is

a) 1,5 times the maximum subatmospheric pressure specified by the manufacturer, or

b) 700 mmHg below atmospheric pressure if the manufacturer's maximum specified subatmospheric pressure exceeds this value.

Testing shall be carried out in accordance with 5.6.1.

4.6.2 Membrane integrity

A test that will detect a blood leak shall be performed on each haemodialyser, haemofilter or haemoconcentrator.

Testing shall be carried out in accordance with 5.6.2.

4.6.3 Blood compartment ports

Except where the haemodialyser, haemofilter or haemoconcentrator and the extracorporeal circuit are designed as an integral system, the dimensions of the blood ports shall be as given in figures 1 and 2.

The dimensions shall be checked in accordance with 5.6.3.

4.6.4 Haemodialyser dialysing fluid compartment ports

The dimensions of the dialysing fluid compartment ports shall be as given in figure 3. In addition, the dialysing fluid compartment port may have a component that will open a self-sealing connector.

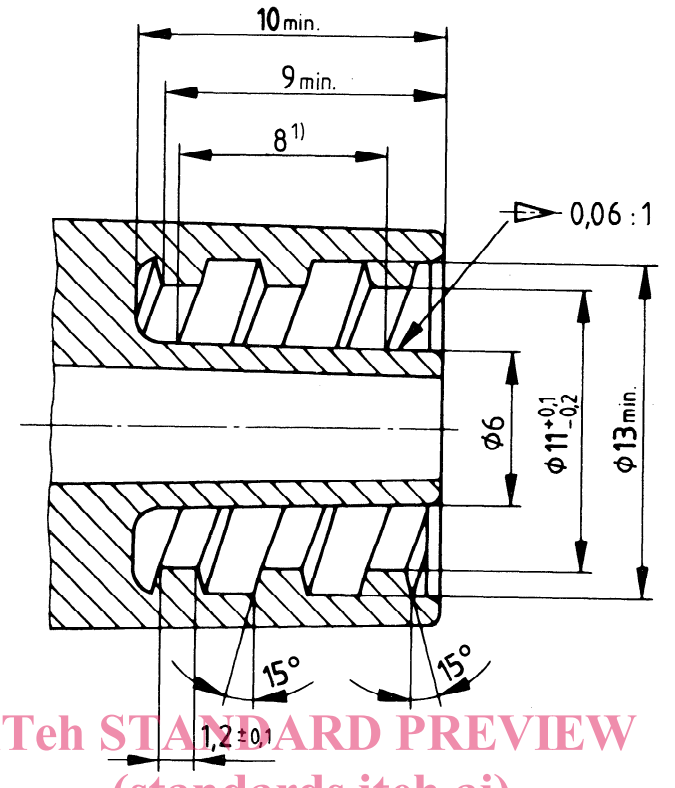
The dimensions of the dialysing fluid compartment ports shall be checked in accordance with 5.6.4.

4.6.5 Haemofilter or haemoconcentrator filtrate port

The haemofilter or haemoconcentrator filtrate port shall meet the requirements specified in 4.6.3 or 4.6.4.

The filtrate port shall be checked in accordance with 5.6.5.

Dimensions in millimetres



1) Double thread.

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

Dimensions in millimetres

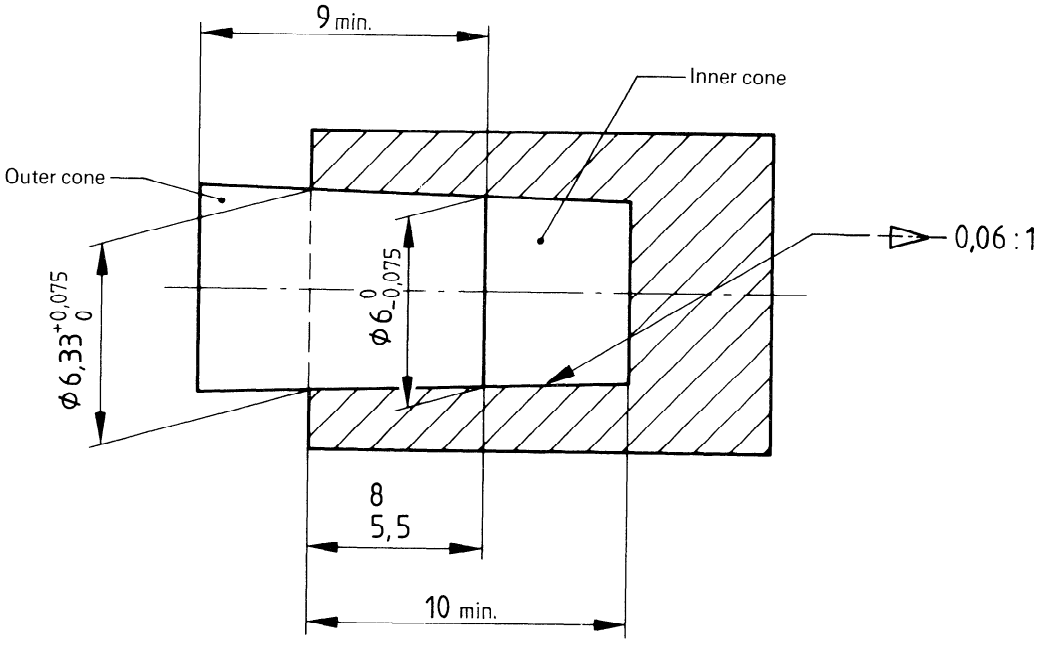


Figure 2 — Length of engagement of male and female cones of blood inlet and outlet connectors

Dimensions in millimetres

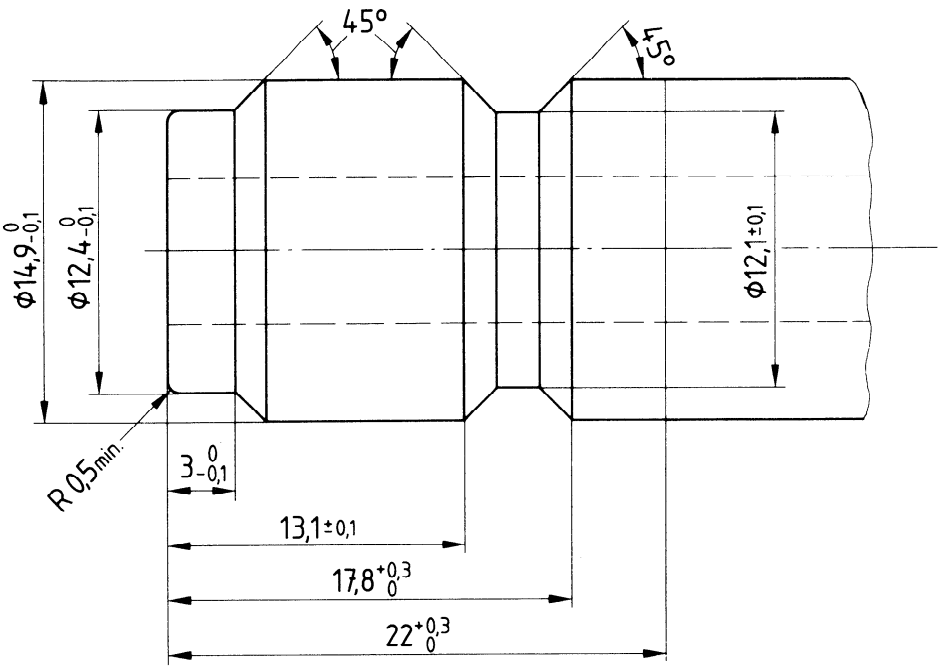


Figure 3 — Main fitting dimensions of dialysing fluid inlet and outlet port

4.7 Disclosure of performance characteristics

4.7.1 General

The performance characteristics specified in 4.7.2 to 4.7.6 shall be determined prior to marketing a new type of device and shall be re-evaluated after changes in the device that may alter its performance.

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

Measurements shall be made *in vitro* at 37 °C ± 1 °C. When the relationship between variables is non-linear, sufficient determinations shall be made to permit interpolation between the data points. The techniques of measurement are referee tests. Other techniques may be used provided that the results are within ±5 % of the technique used in the referee test.

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, outgassing of test fluids, trapped air, and system contamination by foreign material, algae and bacteria.

The following information shall be given in the product literature or the product data sheet:

a) the number of units tested;

b) the mean and standard deviation of measurement for each parameter;

c) the details of change in performance that may occur with duration of observation;

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

4.7.2 Clearance of haemodialysers

The clearance rates of urea, creatinine and vitamin B_{12} shall be stated for the range of blood and dialysing fluid flow rates recommended by the manufacturer and shall include a blood flow rate of 200 ml/min and a dialysing fluid flow rate of 500 ml/min. The filtrate flow rate, q_{V_F}, shall be stated for each condition.

The blood compartment shall be perfused with the test substances dissolved in dialysing fluid. The perfusate shall contain the materials within the range specified below:

Urea:	15 mmol/l to 35 mmol/l
Creatinine:	500 µmol/l to 1 000 µmol/l
Vitamin B_{12}:	15 µmol/l to 40 µmol/l

The dialysing fluid compartment shall be perfused with dialysing fluid. In the case of coil haemodialysers, dialysance shall not be substituted for clearance and, if the former is given in addition, the relationship between the two and the clinical relevance of clearance shall be emphasized. In addition, the recirculation rate through the coil haemodialyser shall be stated.

NOTE — Examples of suitable test circuits are given in figures 4 to 8.

4.7.3 Clearance for haemofilters

The clearance rate of urea, creatinine and vitamin B_{12} shall be stated for the range of blood flow rates recommended by the manufacturer and shall include a blood flow rate of 200 ml/min. The composition of the solution perfusing the blood compartment shall be as specified in 4.7.2.

NOTE — An example of a suitable test circuit is given in figure 8.

4.7.4 Filtration rate

If the relationship between filtration rate and transmembrane pressure or mean coil pressure is non-linear, the filtration rate, expressed in millilitres per hour, shall be given over the manufacturer's stated range of transmembrane pressure or mean coil pressure. If there is a linear relationship between filtration rate and the transmembrane pressure or mean coil pressure, the filtration coefficient shall be stated, expressed in millilitres per hour. The priming pressure shall not exceed the maximum test pressure.

Measurements shall be performed with dialysing fluid perfusing the blood compartment, and, in the case of haemodialysers, no fluid perfusing the dialysing fluid compartment. The sequence of measurement shall be from minimum to maximum transmembrane pressure or mean coil pressure.

NOTE — Examples of suitable test circuits are given in figures 8 and 9.

4.7.5 Volume of blood compartment

The volume of the blood compartment and, if applicable, the dialysing fluid compartment shall be determined with wetted membranes (i.e. a device prepared as recommended by the manufacturer for clinical use) using non-ultrafiltratable liquid, and shall be given at stated conditions over the range of transmembrane pressure or mean coil pressure recommended by the manufacturer.

4.7.6 Hydraulic resistance

The hydraulic resistance of the blood compartment and, if applicable, the dialysing fluid compartment shall be determined using a 32 % (V/V) solution of glycerol and water respectively. These measurements shall be carried out over the range of blood flow rate, dialysing fluid flow rate and transmembrane pressure or mean coil pressure recommended by the manufacturer.