

American National Standard

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Hemodialyzers



**Association for the Advancement
of Medical Instrumentation**

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American National Standard

ANSI/AAMI RD16—1996 (Revision of ANSI/AAMI RD16—1984)

Hemodialyzers

Developed by

Association for the Advancement of Medical Instrumentation

Approved 8 March 1996 by

American National Standards Institute, Inc.

Abstract:

This standard establishes labeling requirements, safety and performance requirements, and tests for hemodialyzers in the purification of the blood by diffusion and convection between the blood and a solution of chemicals through a semipermeable membrane.

Committee representation

Association for the Advancement of Medical Instrumentation

AAMI Renal Disease and Detoxification Committee

This proposed draft standard was revised by the Renal Disease and Detoxification Committee of the Association for the Advancement of Medical Instrumentation. Committee approval of the standard does not necessarily imply that all committee members voted for its approval.

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Acknowledgment

The Committee gratefully acknowledges the contributions of the late James Dugan, Gulfstream Medical, whose input and assistance contributed to the writing of this document.

NOTE—Participation by federal agency representatives in the development of this standard does not necessarily constitute endorsement by the federal government or any of its agencies.

Foreword

This voluntary standard was developed by the Renal Disease and Detoxification Committee of the Association for the Advancement of Medical Instrumentation, in cooperation with the American Society for Artificial Internal Organs and the Health Industry Manufacturers Association. In addition, representatives of many other medical, technical, and patient organizations, as well as representatives of government agencies, contributed to this effort.

This standard reflects the conscientious efforts of concerned physicians, clinical engineers, nurses, dialysis technicians, and patients, in consultation with device manufacturers, to develop a standard for those performance levels that could be reasonably achieved as of this writing. The term "consensus," as applied to the development of voluntary medical device standards, does not imply unanimity of opinion; rather, it reflects the compromises that are often necessary when a variety of viewpoints and interests must be merged.

This AAMI medical device standard is addressed to the manufacturer of the device but will also affect the user of the device. The committee agrees with the Center for Devices and Radiological Health, U.S. Food and Drug Administration, that the manufacturer's responsibility is limited to providing a safe, effective device with appropriate recommendations for the first use of the device. Subsequent uses of the device for a single patient after reprocessing (dialyzer reuse) are the responsibility of the patient's physician. Current efforts by the Center for Devices and Radiologic Health to require relabeling of hemodialyzers, recognizing the near general practice of reuse, are of uncertain status. These plans would require manufacturers to include guidance for this practice and warnings about incompatible or hazardous materials or procedures that might be used to reprocess a dialyzer. This document will not address that issue but does address dialyzer performance not strictly limited to first use, thus "first use" was dropped from the title of the standard. The committee recognizes that financial considerations and/or perceived benefits to the patient may lead the user to decide to undertake the multiple use

of hemodialyzers.

In some cases, multiple uses of a hemodialyzer may actually facilitate the hemodialysis procedure. The committee, through the AAMI Hemodialyzer Reuse Subcommittee, has produced a guideline for clinicians reprocessing dialyzers for reuse (ANSI/AAMI [RD47-1993](#)) and directs the reader to that document for further information.

As used within the context of this document, "shall" indicates requirements strictly to be followed in order to conform to the recommended practice; "should" indicates that among several possibilities one is recommended as particularly suitable, without mentioning or excluding others, or that a certain course of action is preferred but not necessarily required, or that in the negative form, a certain possibility or course of action is avoided but not prohibited; "may" is used to indicate that a course of action is permissible within the limits of the recommended practice; and "can" is used as a statement of possibility and capability. "Must" is used only to describe "unavoidable" situations, including those mandated by federal regulation.

Suggestions for improving this standard are invited. Comments and suggested revisions should be sent to AAMI, 3330 Washington Boulevard, Suite 400, Arlington, VA 22201-4598.

NOTE—This foreword is not part of the American National Standard for Hemodialyzers (ANSI/AAMI RD16-1996).

Hemodialyzers

1 Scope

1.1 General

For purposes of this standard, a hemodialyzer is defined as an extracorporeal device that changes the chemical composition of the blood by diffusion and convection of substances between the blood and a solution of chemicals through a semipermeable membrane. Furthermore, a hemodialyzer functions within clinically acceptable rates of water and solute transport. Use of the device is indicated in the treatment of severe renal insufficiency and in the removal of certain toxic substances. For purposes of this standard, hemodialyzers are limited to those ready for use upon manufacture; the responsibility of the manufacturer is limited to the use of the hemodialyzer as labeled.

1.2 Inclusions

Included within the scope of this standard are ready-to-use hemodialyzers of parallel plate and hollow fiber design. These hemodialyzers are commonly used in clinical practice.

1.3 Exclusions

Excluded from the scope of this standard are hemodialyzers that are assembled from component parts by the user and accessory devices attached to the hemodialyzer or used in the complete assemblage of devices for the hemodialysis procedure. Examples of types of devices excluded from the scope of this standard are: separate tubings that connect the hemodialyzer to the blood access devices, reagents used for the dialysate, blood access devices, hemodialysis systems that prepare, maintain, or monitor the dialysate, pumps that circulate the patient's blood through the hemodialyzer, devices that infuse substances such as heparin or protamine during dialysis, peritoneal dialysis devices, hemofiltration devices, hemoperfusion devices, and plasmapheresis devices. The acceptable ranges in test methods for pediatric dialyzers may be less than those specified in this document.

NOTE—A rationale for the development of this standard, including a statement of the need for the standard as well as rationale for the specific provisions of the standard, is provided as [annex A](#).

2 Normative references

The following documents contain provisions, which, through reference in this text, constitute provisions of this AAMI standard. At the time of publication, the editions indicated were valid. All documents are subject to revision, and parties to agreements based on this AAMI standard are encouraged to investigate the possibility of applying the *most recent editions* of the documents listed below.

2.1 Association for the Advancement of Medical Instrumentation. *Recommended Practice for Determining Residual Ethylene Oxide in Medical Devices*. ANSI/AAMI ST29-1988. Arlington (Vir.): AAMI, 1988. American National Standard. (Other standard.)

2.2 Association for the Advancement of Medical Instrumentation. *Recommended Practice for Determining Residual Ethylene Chlorohydrin and Ethylene Glycol in Medical Devices*. ANSI/AAMI ST30-1988. Arlington (Vir.): AAMI, 1988. American National Standard. (Other standard.)

2.3 *Code of Federal Regulations*, Title 21, Part 820, "Good Manufacturing Practice for Medical Devices."

2.4 *Code of Federal Regulations*, Title 21, Part 876, "Classification of Gastroenterology-Urology Devices," Subpart F—Therapeutic Devices (21 CFR 876.5820): Hemodialysis Systems and Accessories.

2.5 *Code of Federal Regulations*, Title 21, Subchapter H, Part 801, "Labeling," and Section 502(a) of the Federal Food, Drug, and Cosmetic Act.

2.6 Food and Drug Administration. *Guidelines for Premarket Testing of New Conventional Hemodialyzers, High Permeability Hemodialyzers and Hemofilters*. Rockville, Md: Office of Device Evaluation, Center for Devices and Radiological Health, Food and Drug Administration, Department of Health and Human Services, March 1982.

2.7 Food and Drug Administration. *Federal Register*. Vol. 43, No. 122, 6/23/78, p. 27482.

2.8 International Organization for Standardization. *Haemodialysers, haemofilters, and haemoconcentrators*. ISO 8637:1989 (1st edition).

2.9 United States Pharmacopeia. Transfusion and Infusion Assemblies; Bacterial Endotoxins Test or Pyrogen Test. United States Pharmacopeia (XXIII). Easton, Penn: Mack Publishing, 1990.

2.10 International Organization for Standardization. *Biological evaluation of medical devices - Part 1: Guidance on selection of tests*. ANSI/AAMI/ISO 10993-1:1992.

2.11 International Organization for Standardization. *Biological evaluation of medical devices - Part 4: Selection of tests for interactions with blood*. ANSI/AAMI/ISO 10993-4:1992.

3 Definitions

For the purposes of this standard, the following definitions apply:

3.1 "arterial" (inlet) blood tubing: The blood tubing connecting the blood access device (needle or cannula) to the blood inlet port of the hemodialyzer.

3.2 blood access device: A device, such as a needle inserted into a vein or a cannula installed in an artery or a vein, that connects the bloodstream of the patient to the blood tubing leading to the hemodialyzer.

3.3 blood compartment: The passage(s) containing the patient's blood in a hemodialyzer during clinical dialysis.

3.4 blood flow rate: The volume of fluid passing through the blood compartment of a hemodialyzer per unit of time.

3.5 C_{Bi}: The concentration of a solute in the fluid entering the blood compartment of the hemodialyzer.

3.6 C_{Bo} : The concentration of a solute in the fluid leaving the blood compartment of the hemodialyzer.

3.7 C_{Di} : The concentration of a solute in the fluid entering the dialysate compartment of the hemodialyzer.

3.8 clearance: A measure of net flux of solute across the hemodialyzer membrane, expressed as the number of ml of blood completely cleared of a solute. For purposes of this standard, clearance includes clearance due to ultrafiltration. (See below for the equations used to calculate clearance.)

3.9 clearance (convective), closed-loop system:

$$K = Q_{UF} \left[\frac{bt}{\ln (1 - Q_{UF}t / V_0)} + 1 \right]$$

where:

b = slope of the regression analysis of the time elapsed and the natural logarithm of the concentration of the test solution;

t = elapsed time ($t_1 - t_0$), in minutes;

V_0 = volume of "patient" reservoir at t_0 ;

Q_{UF} = ultrafiltration rate.

3.10 clearance (diffusive & convective), open-loop system:

$$K = \frac{(C_{Bi} - C_{Bo}) Q_{Bi}}{C_{Bi}} + \frac{C_{Bo} Q_{UF}}{C_{Bi}}$$

where:

C_{Bi} = the concentration of a solute in the fluid entering the blood compartment of the hemodialyzer;

C_{Bo} = the concentration of a solute in the fluid leaving the blood compartment of the hemodialyzer;

Q_{Bi} = blood flow rate entering the hemodialyzer;

Q_{UF} = ultrafiltration rate.

3.11 closed-loop system: A test system for hemodialyzer performance in which a reservoir of fluid is recirculated through the dialyzer throughout the test.

3.12 convection: Transport of solutes as components of a solution passing through a semipermeable membrane along a pressure gradient.

3.13 dialysate: The electrolyte solution used to make a concentration gradient between the solution and blood in the hemodialyzer. Also termed the dialyzing fluid.

3.14 dialysate flow rate: The volume of fluid passing through the dialysate compartment per unit of time.

3.15 diffusion: Transport of solutes through a semipermeable membrane along a concentration gradient.

3.16 hemodialyzer: A device, commonly referred to as an artificial kidney, which transports components of the blood by diffusion and convection through a semipermeable membrane.

3.17 hemofiltration device: A device that transports components of the blood by convection through a semipermeable membrane.

3.18 high-efficiency dialyzers: Characterized by high clearances of small molecules (e.g., urea) accomplished by large surface area. Clearances may increase with high blood and dialysate flows.

3.19 high-flux dialyzers: Characterized by removal of large molecules (≥ 8000 daltons, for example, B₂ microglobulin) by diffusion, convection, or adsorption.

3.20 K: Clearance in milliliters per minute (ml/min).

3.21 manufacturer: The party responsible for the quality control of a product.

3.22 metrology program: A program that assures accuracy and proper performance of measurement and control equipment and thus assures validity of test results. The accuracy of this program's calibration standards can be traced back to recognized standards at the National Institute of Standards and Technology.

3.23 negative pressure: Subatmospheric pressure.

3.24 nonpyrogenic: Free of fever-producing materials within the limit of error of test methods for such determinations as per USP.

3.25 open-loop system: A test system for hemodialyzer performance in which the solutions perfusing the hemodialyzer are discharged to drain after one passage through the hemodialyzer.

3.26 P_{Bi}: Pressure at the arterial (inlet) port of a hemodialyzer blood compartment.

3.27 P_{Bo}: Pressure at the venous (outlet) port of a hemodialyzer blood compartment.

3.28 P_{Di}: Pressure at the inlet port of a hemodialyzer dialysate compartment.

3.29 P_{Do}: Pressure at the outlet port of a hemodialyzer dialysate compartment.

3.30 Q_{Bi}: Blood flow rate entering the hemodialyzer.

3.31 Q_{Bo}: Blood flow rate leaving the hemodialyzer.

3.32 Q_{Di}: Dialysate flow rate entering the hemodialyzer.

3.33 Q_{Do}: Dialysate flow rate leaving the hemodialyzer.

3.34 Q_i: Flow rate of air entering the hemodialyzer.

3.35 Q_o: Flow rate of air leaving the hemodialyzer.

3.36 Q_{UF}: Ultrafiltration rate.

3.37 semipermeable membrane: A membrane that permits transport of some solutes while retaining others, such as the formed elements of blood, and large molecules.

3.38 sterile: Free of living microbial organisms within the limit of error of test methods for such determinations. Accepted as sterile by methods of good manufacturing practices. A demonstration that the likelihood of viable organisms present is $< 10^{-6}$.

3.39 TMP: Transmembrane pressure.

3.40 transmembrane pressure: The pressure exerted across the semipermeable membrane, which can be expressed by the equation:

$$\text{TMP} = (\text{P}_{\text{Bi}} + \text{P}_{\text{Bo}})/2 - (\text{P}_{\text{Di}} + \text{P}_{\text{Do}})/2$$

3.41 ultrafiltration control hemodialysis system: A machine capable of accurately monitoring and controlling the volume of ultrafiltrate directly through electronic, mechanical, or hydraulic means. Must provide acceptable safety for use with high ultrafiltration dialyzers.

3.42 user: For the purposes of this standard, the physician or medical professional, not the patient (as would be the case in home dialysis, where the "user" is also the patient). This medical device standard is directed to the manufacturer of the device and therefore the user is the physician or his or her representative.

3.43 "venous" (outlet) blood tubing: The blood tubing connecting the hemodialyzer blood compartment outlet to the blood access device (needle or cannula).

4 Requirements

4.1 Labeling and documentation requirements

The term "labeling" in this standard includes any written material accompanying a hemodialyzer or its container.

4.1.1 Device markings

Each device shall exhibit the following minimum information:

- a) the name and address of the manufacturer;
- b) the trade name (if any) and generic name (e.g., hemodialyzer) of the product;
- c) the manufacturer's identifying (catalog) number;
- d) an identifying lot or control number that provides complete traceability of the manufacturing history of the device;
- e) the date of sterilization accurate within 30 days;
- f) identifying markings that readily distinguish the device from similar devices made by the same manufacturer;
- g) identification of blood inlet port, blood outlet port, dialysate inlet port, and dialysate outlet port;
- h) a statement that an ultrafiltration control machine is required, if necessary.

4.1.2 Shipping container

Each shipping container shall display or have enclosed all of the information required in 4.1.1, in addition to the following:

- a) the date of sterilization accurate within 30 days;
- b) a statement concerning the sterility and nonpyrogenicity of the product, such as "Contents sterile and nonpyrogenic provided seal and container intact" or "Sterile and nonpyrogenic blood path only," as appropriate;
- c) special conditions of storage and handling;
- d) the statement or similar language, "Caution: Federal (USA) law restricts this device to sale by or on the order of a physician";
- e) a statement such as, "Caution: See Directions for Use before using this device";
- f) other descriptive information, warnings, or precautions that are deemed appropriate by the manufacturer and that will conveniently fit within the space limitations of the label.

4.1.3 Package insert/instructions for use

Each shipping container of hemodialyzers shall be accompanied by a Directions for Use insert. The insert shall include at least the following, as appropriate:

a) instructions for preparing the hemodialyzer for operation and recommendations for performing dialysis, including, at a minimum:

1) a statement such as, "Inspect packages for damage before use;"

2) detailed, step-by-step instructions for preparing the hemodialyzer for clinical use, covering rinsing and priming procedures and any applicable tests for residual sterilants, with an explanation of the rationale for the tests (e.g., the need to remove potentially hazardous materials) where appropriate (diagrams for dialysis set-up are desirable);

3) recommended operating conditions;

4) recommended procedures in the event of known complications, such as blood-to-dialysate leaks, dialysate compartment leaks, blood loss or air embolism, excessive pressure drop across the hemodialyzer, or clotting;

5) procedures for terminating dialysis and, as appropriate, special conditions for disposal of the hemodialyzer.

b) a warranty for first use, including

1) general limits and conditions of warranty;

2) a statement to the effect that "The manufacturer assures the sterility of the device for the first use only and only when undamaged and prepared and used as recommended";

3) if the device is labeled for reuse, a note that information regarding reuse is available upon request.

c) a description of the hemodialyzer, including nominal volume of the blood compartment, compliance of the blood compartment (if applicable), the nominal surface area, the type of membrane, and the specifications of the blood tubing connectors and dialysate port connectors;

d) the usual indications for use recommended by appropriate medical authorities;

e) a list of known adverse reactions (when applicable to the specific device or its materials of composition), such as pyrogenicity, hypersensitivity, etc.;

f) general and specific contraindications, if appropriate;

g) the method of sterilization (e.g., ethylene oxide sterilization, steam, or gamma irradiation);

h) appropriate warnings if the design of the dialyzer can lead to flow maldistribution, either below certain blood or dialysate flow rates or because of its operation in an inappropriate position (e.g., vertical, horizontal);

i) any particular features that significantly distinguish the hemodialyzer from other hemodialyzers of the same general type;

j) the ranges of blood flow rate, dialysate flow rate, transmembrane pressure, temperature, and any other important operating conditions recommended by the manufacturer for safe and efficacious performance of the device;

k) a statement that ultrafiltration control systems are required, if appropriate;

l) information concerning the characteristics of the first-use hemodialyzer:

NOTE—In general, the information contained in the following paragraphs ("1" through "4") shall provide

the physician with data regarding the clinical application of the device. The methods used shall be available upon request.

1) the ultrafiltration coefficient in ml/h/mmHg transmembrane pressure (TMP) shall be defined as the slope of the ultrafiltration rate versus TMP between ultrafiltration rates of 600 ml/h and 1800 ml/h. The test methodology shall be defined. If *in vitro* data are presented, a method of estimating *in vivo* performance shall be provided or available. For those dialyzers capable of being run on machines without ultrafiltration control, it is suggested that the information also be presented graphically. The data is considered valid only within the specified range. If the ultrafiltration coefficient varies by more than $\pm 20\%$ this information shall be disclosed;

2) *in vitro* clearances for urea, creatinine, and vitamin B₁₂ in ml/min; results should be given for the manufacturer's recommended range of blood flow rates (i.e. not only 200 ml/min); results should be given also for the manufacturer's range of dialysate flow rates (e.g., 500-1000 ml/min); *in vitro* urea clearance should be within 10% of the manufacturers' stated value at a blood flow of 200 ml/min and a dialysate flow of 500 ml/min or other stated conditions. Variations will increase at higher flows;

3) blood compartment volume, expressed as ml; the technique of measurement; if appropriate, the blood compartment volume shall be given for blood flow rates spanning the manufacturer's recommended range, with TMP spanning the manufacturer's recommended range;

m) a list of the generic names of materials in contact with the blood or dialysate (if this information is not provided in the product data sheet);

n) a description of chemicals and processes used routinely in clinical practice that are known to have adverse effects on dialyzer materials;

o) a statement that the following are available to the user upon request:

1) details of the test methodologies;

2) results (if available) of clinical performance tests;

3) the number and range of particulates and fibers in the effluent from the hemodialyzer, when prepared as recommended for clinical use;

4) results of toxicological investigations and tests.

4.2 Performance requirements

Each of the following parameters shall be measured *in vitro* for hemodialyzers (prepared as recommended for clinical use and at the recommended operational temperature) using aqueous solutions, unless otherwise noted.

4.2.1 Ultrafiltration coefficient

In vitro ultrafiltration coefficient information shall be determined under the conditions defined in 4.1.3(1)(1) and expressed as specified in that section.

4.2.2 Solute clearance

In vitro clearance shall be determined for the substances and under the conditions defined in 4.1.3(1)(2) and expressed as specified in that section. Changes in pressure over the manufacturer's recommended range shall not cause more than a $\pm 10\%$ variation in clearance.

4.2.3 Blood compartment volume and compliance

In vitro blood compartment volume shall be determined under the conditions specified in 4.1.3(1)(4). Volume changes due to pressure changes shall be measured if they have a significant effect on the volume of the

hemodialyzer or on dialyzer performance.

4.3 Mechanical/structural integrity requirements

Functional tests of clearance and ultrafiltration coefficient are to be performed on final sterilized product.

4.3.1 General structural integrity

Hemodialyzers selected at random from production models that have passed all safety and quality control tests shall withstand a pressure 1.5 times the maximum recommended positive operating pressure and a negative pressure that is 1.5 times the maximum recommended negative pressure, or 700 mmHg, whichever is less. The test system shall include the blood tubing connections.

4.3.2 Membrane integrity

Each hemodialyzer shall be tested by a method capable of detecting a blood leak.

4.3.3 Package integrity

The hemodialyzer shall be packaged to minimize damage during shipping and storage.

4.4 Device cleanliness/requirements for materials

4.4.1 Sterility and nonpyrogenicity

The blood pathway shall be demonstrated to be sterile and nonpyrogenic in manufacture. If delivered to the user unopened and undamaged, it may be considered to remain so. The dialysate pathway shall be sterilized as a concomitant of blood path sterilization, but tests for sterility and pyrogenicity need not be carried out.

4.4.2 Material safety

Any component material of the hemodialyzer that will be in contact with blood or dialysate shall be shown to be not toxic as per 2.10 and 2.11.

4.4.3 Residual ethylene oxide

Residual ethylene oxide, ethylene chlorohydrin, and ethylene glycol shall be no greater than limits proposed by the FDA Federal Register, vol. 43, No. 122, 6/23/78, p. 27482.

Ethylene oxide 25 parts per million (ppm)

Ethylene chlorohydrin 25 (ppm)

Ethylene glycol 250 (ppm)

If the FDA establishes different standards, these devices shall meet the required FDA standards.

4.5 Tubing connectors

4.5.1 Blood port

Blood ports shall meet the requirements of the ISO International Standard *Cardiovascular implants and artificial organs - Haemodialysers, haemofilters and haemoconcentrators* (ISO 8637)¹ with the exception of the internal diameter.

4.5.2 Dialysate port

Dialysate ports of the hemodialyzer assembly shall meet the requirements of the ISO International Standard *Cardiovascular implants and artificial organs— Haemodialysers, haemofilters and haemoconcentrators* (ISO 8637)² with the exception of the internal diameter.

5 Tests

This section contains test methods that may be used to establish and verify the performance characteristics of hemodialyzers. Test methodologies other than those presented here may be used if the test facility establishes that the results obtained are equivalent to results that would be obtained if the methods of this standard were used.

The methods and procedures presented are intended for initial product qualification, for periodic revalidation of stated product claims, and for determining compliance with section 4 of this standard. They are not intended for routine quality control.

The test systems shown are simplified structures and, therefore, do not show all of the necessary details of practical test apparatus. The design and construction of actual test systems and the establishment of practical test procedures shall not only be based on these ideal set-ups, but adequately address the many factors contributing to measurement error, including, but not limited to, outgassing of test fluids; trapped air; uncontrolled temperature variations; nonconstant flow rates; degradation of test substances with heat, light, and time; system contamination by foreign material, algae, and bacteria; pressure measurement errors due to static head effects and dynamic pressure drops; and parameter stabilization times.

All instruments used to measure physical quantities, including length, mass, volume, flow rate, concentration, and pressure, shall be regularly maintained and calibrated in accordance with an ongoing metrology program traceable to the calibration standards of the National Institute of Standards and Technology.

NOTE—Definitions of terms and mathematical symbols not provided in this section are given in section 3, Definitions. The paragraph numbers of this section correspond with the paragraph numbers of section 4, except for the first digit.

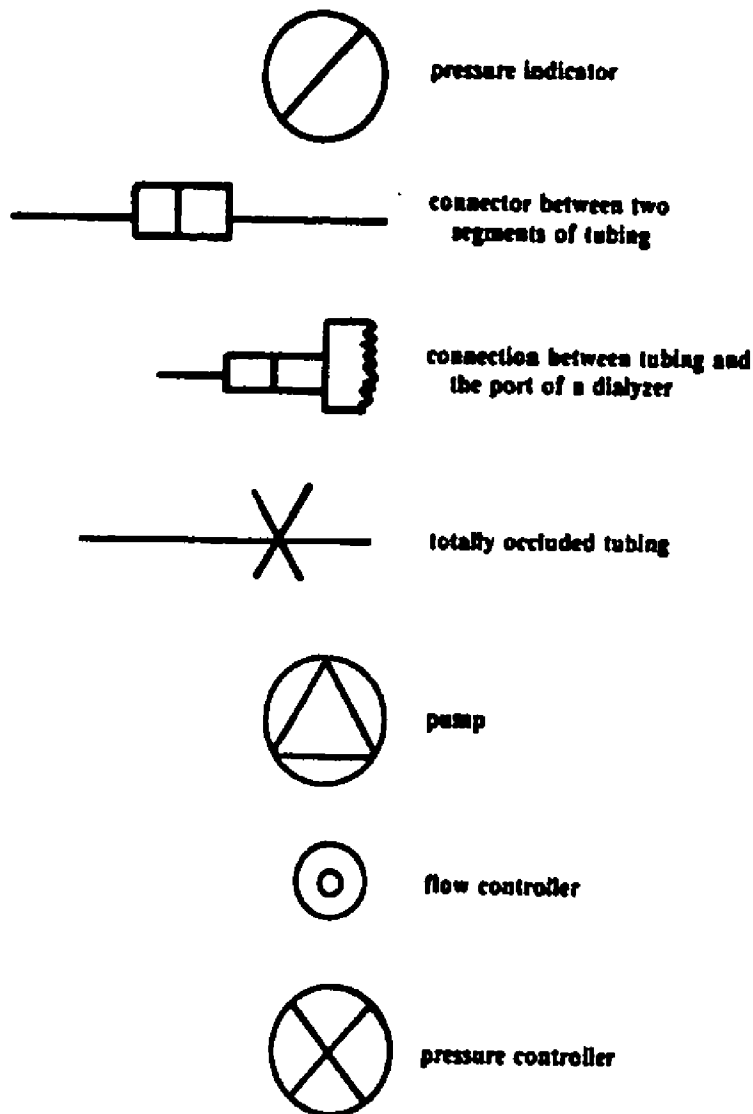
5.1 Labeling and documentation requirements

Compliance with the requirements of section 4.1 can be determined by visual inspection.

5.2 Performance requirements

More than one of the following tests may be performed at the same time, using the same hemodialyzer and test apparatus. If this is done, however, the sequence of tests shall be such that the reliability of any test is not adversely influenced by the test sequence.

The connections referenced in 4.5 shall be used to connect the test tubing to the blood and dialysate ports of the hemodialyzer. The temperature of the perfusate shall be $37^{\circ} \pm 1.5^{\circ}$ C. Reservoirs shall be calibrated so that measurements over the period of observation vary by $\pm 2\%$ or less. The error of graduated cylinders shall be at most $\pm 2\%$. Flow rates shall be determined by flow meters with a maximum error of $\pm 2\%$. Reservoirs and pumps other than those commonly used in clinical dialysis may be used, provided that they in no way diminish the accuracy of the measurements. In the figures, the following symbols are used:



Prior to evaluation, each hemodialyzer shall be prepared according to the manufacturer's directions for use; blood compartment integrity shall be verified by means of an air test capable of detecting any defect that would result in a blood leak at a blood compartment pressure of +300 mm Hg; and dialysate compartment integrity shall be verified by means of an air test capable of detecting an air leak of 1 ml/min at a dialysate compartment pressure of +300 mmHg.

Suitable methods for air leak testing of hemodialyzers are depicted in [figures 1 and 2](#). The membrane may be wet or dry for this test. Adequate time shall be allowed for the system to stabilize before the tests are made.

5.2.1 Ultrafiltration coefficient

Testing is begun after the dialyzer membranes have been wetted for at least 10 min. At this time, the dialysate flow is discontinued, the initial outflow from the dialysate compartment is discarded, and the subsequent effluent from the dialysate compartment is collected in a graduated cylinder. The rate of fluid leaving the dialysate compartment is the ultrafiltration rate. A suitable circuit for hemodialyzers is shown in [figure 3](#). The conditions of measurement are given in [4.1.3\(l\)\(1\)](#). For dialyzers containing membranes with low hydraulic permeability, the pump in the outflow line from the dialysate compartment may be omitted from the circuit. In this case, the TMP is increased by steps, and the ultrafiltration rate is recorded at each step. For dialyzers

containing membranes with higher hydraulic permeabilities, it may not be possible to control the ultrafiltration rate over the required range by changing TMP. In this case, the pump in the outflow line from the dialysate compartment is used to vary the ultrafiltration rate over the required range, and the TMP is recorded for each ultrafiltration rate.

5.2.2 Solute clearance

The solute clearance characteristics of the hemodialyzer shall be determined at the conditions specified in 4.1.3(1)(2). Either a closed- or an open-loop system may be used. Figure 4 depicts test circuits for closed-loop testing of hemodialyzers.

The "patient" circuit shall be well mixed and large enough that it cannot be emptied by ultrafiltration during the test. Figure 5 shows a test circuit for open-loop testing of hemodialyzers designed for single-pass dialysate systems.

The dialysate circuit shall contain dialysate. The "patient" circuit shall contain a solution of dialysate and test substance(s) whose initial concentrations shall be as shown in Table 1, except that higher concentrations may be used to achieve a suitable reservoir volume in the closed-loop method.

Table 1—Concentration of Substances Used for Solute Clearances

Solute	Molecular Weight (MW)	Concentration (mg/dl)
Urea	60	100
Creatinine	113	10
Vitamin B ₁₂ (Cyanocobalamin)	1355	5

When the closed-loop system is used, the test is conducted by stabilizing the system at the minimum blood flow rate and at the appropriate dialysate flow rate for at least 10 min at a specified TMP or ultrafiltration rate. The rate of decline of the reservoir is noted serially in order to determine the ultrafiltration rate. Enough serial samples are taken from the "patient" reservoir to perform a regression analysis of the time elapsed and the natural logarithm of the concentration of the test solution. The clearance is determined from the equation given in section 3 as part of the definition of "clearance-closed loop." This procedure is repeated for each "blood" flow rate.

When the open-loop system is used, the "patient" circuit shall be perfused with a solution of dialysate containing urea (MW 60) at an initial concentration of 100 mg/dl. Higher concentrations may be used to achieve a suitable reservoir volume in the closed-loop method. Hemodialyzers that have been tested for ultrafiltration by the method of 5.2.1 shall be used. Dialysate shall be used to perfuse the dialysate circuit. The test is conducted by stabilizing the system for at least 10 min and then sampling both the fluid entering the "blood" compartment of the hemodialyzer (C_{Bi}) and the fluid leaving the blood compartment (C_{Bo}). The ultrafiltration rate is determined by the relationship between ultrafiltration and TMP for the hemodialyzer. This procedure is repeated for each "blood" flow rate.

Clearance is calculated from the equation given in section 3 as part of the definition of "clearance-open loop."

(See A.4.2.2 for cytochrome C and beta-2 microglobulin clearance testing.)

5.2.3 Blood compartment volume and compliance

The blood volume measurement for the noncompliant hemodialyzers: after membranes are wetted for at least 10 min, both blood and dialysate compartments are filled with an aqueous solution and dialysate ports are capped.

Fluid expelled from the blood compartment with air is collected and measured as the blood path volume.

5.3 Mechanical/structural integrity

5.3.1 General structural integrity

Testing is begun after the dialyzer membranes have been wetted for at least 10 min. The connectors specified in 4.5.1 shall be used for the blood port connections. These tests require a connection to the dialysate port capable of withstanding the test pressure. (The integrity of the dialysate connector specified in 4.5.2 is verified by the air test of 5.2 for hemodialyzers.)

a) **Positive Pressure Test.** The circuit shown in figure 6 shall be used for hemodialyzers. After the blood and dialysate compartments are perfused with dialysate at 37° C for at least 10 min, the dialysate compartment ports and one of the blood compartment ports are clamped. The dialyzer is then pressurized to 1.5 times the recommended maximum pressure for 10 min. An unsatisfactory test result is evidenced by visible leakage or the inability of the hemodialyzer to achieve the test pressure.

b) **Negative pressure Test.** The dialyzer is prepared as described in 5.3.1(a), using adequately deaerated fluid in the blood compartment. The blood lines and one of the dialysate lines are then clamped. The negative pressure is applied to the other dialysate line (see figure 7) for 10 min. The negative pressure shall be 1.5 times the manufacturer's recommended maximum negative pressure, unless that pressure is more than 700 mmHg below atmospheric pressure at sea level. In that case, the pressure shall be 700 mmHg below atmospheric pressure at sea level. A satisfactory result is evidenced by a stable pressure without the appearance of air in the visible fluid paths.

5.3.2 Membrane integrity

Figure 1 depicts a test circuit for dialyzers. Dialyzers (which must already have passed the air test) are said to have passed the test for membrane integrity if they do not leak when perfused with blood. This validation is done only for selected dialyzers during design qualification; it is not done on each dialyzer for quality control.

5.3.3 Package integrity

Compliance with this requirement can be verified by visual inspection.

5.4 Device cleanliness/requirements for materials

5.4.1 Sterility and nonpyrogenicity

Sterility shall be assured by compliance with Good Manufacturing Practices (GMP) regulations for medical devices. Nonpyrogenicity shall be determined by testing appropriate samples by means of the USP pyrogen test or bacterial endotoxins test (Normative Reference 2.9) or an alternate test approved by the Center for Devices and Radiological Health.

5.4.2 Material safety

Any component material of the hemodialyzer that will be in contact with blood or dialysate shall be shown to be not toxic as per 2.10 and 2.11.

5.4.3 Residual ethylene oxide

Residual ethylene oxide shall be determined by appropriate methodology to the limits promulgated by federal regulations. Reference may be made to the AAMI *Recommended Practice for Determining Residual Ethylene Oxide in Medical Devices* (Normative Reference 2.1).

5.5 Tubing connectors

Compliance with the requirements of 4.5 can be verified by inspection.

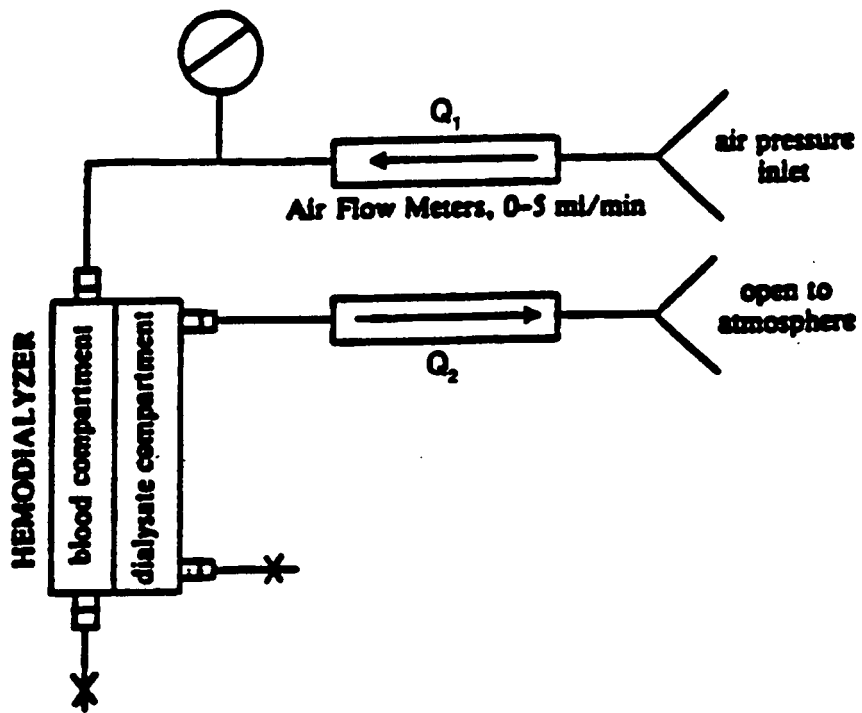


Figure 1—Blood compartment/membrane leak test

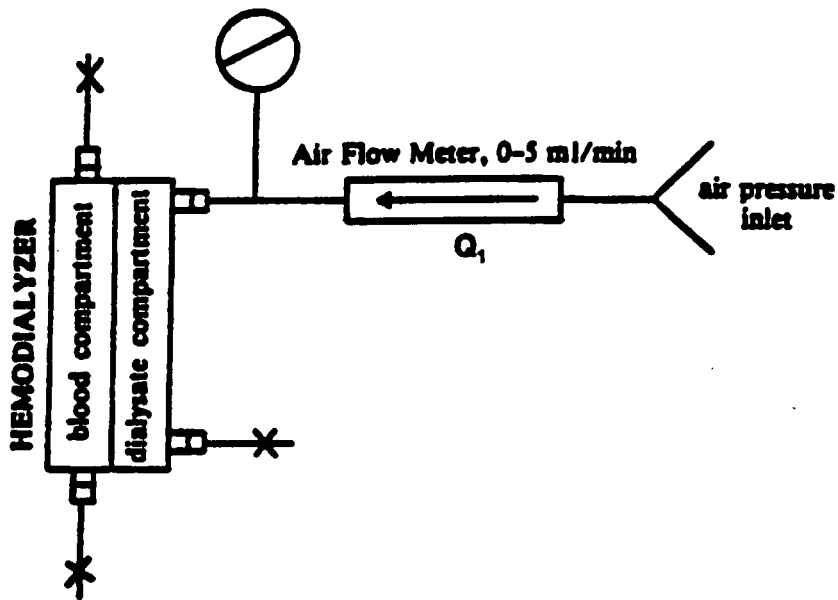


Figure 2—Dialysate compartment leak test

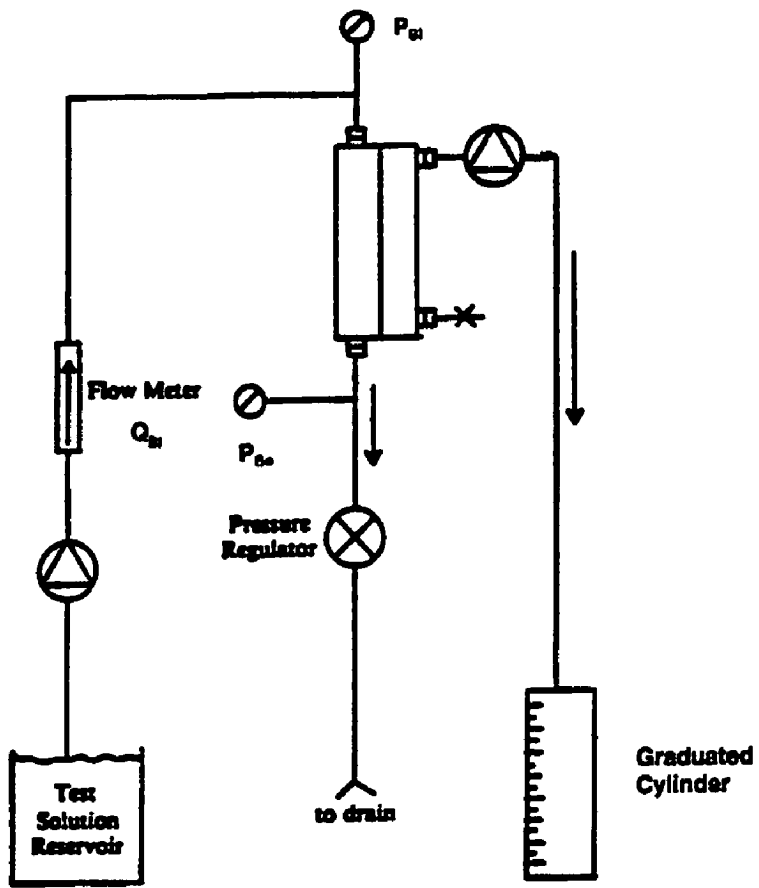


Figure 3—Test system for ultrafiltration

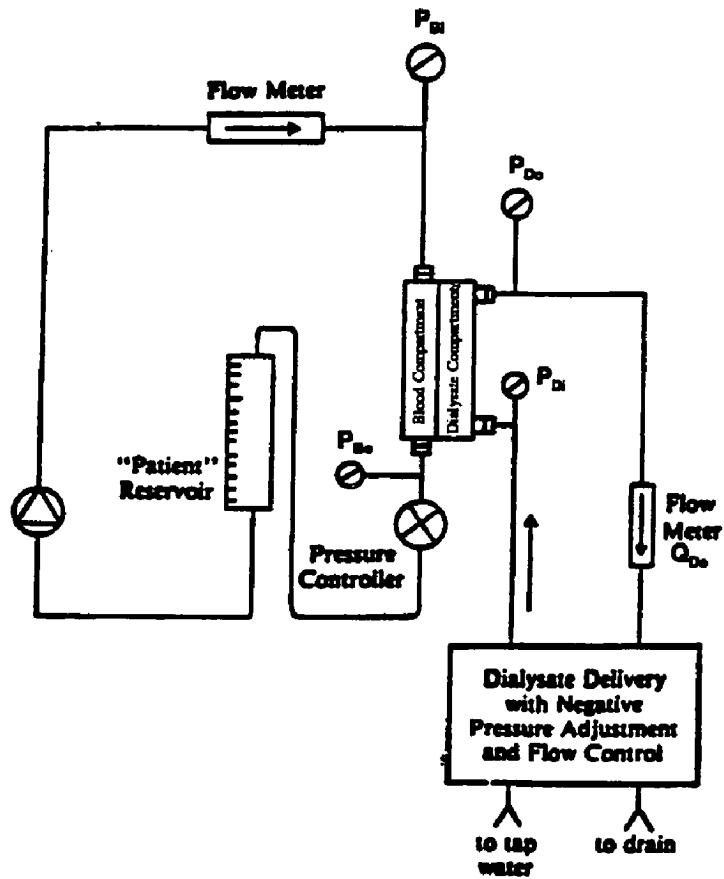


Figure 4—Closed-loop test system

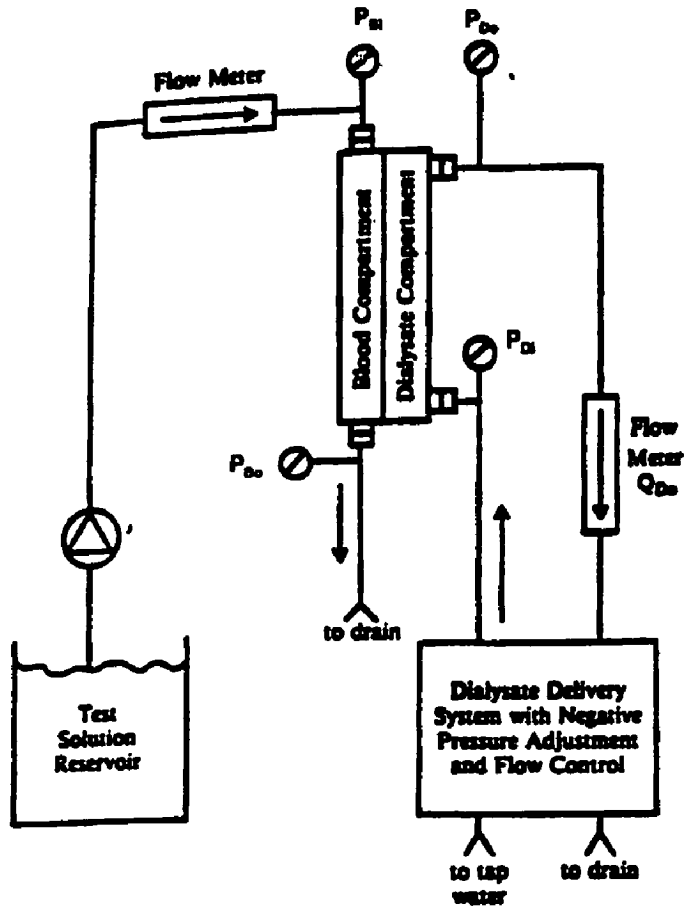


Figure 5—Open-loop test system

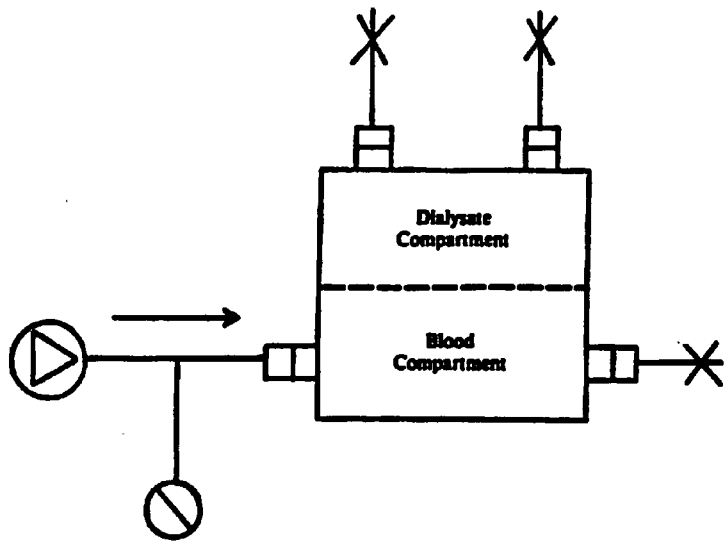


Figure 6—System for positive pressure testing

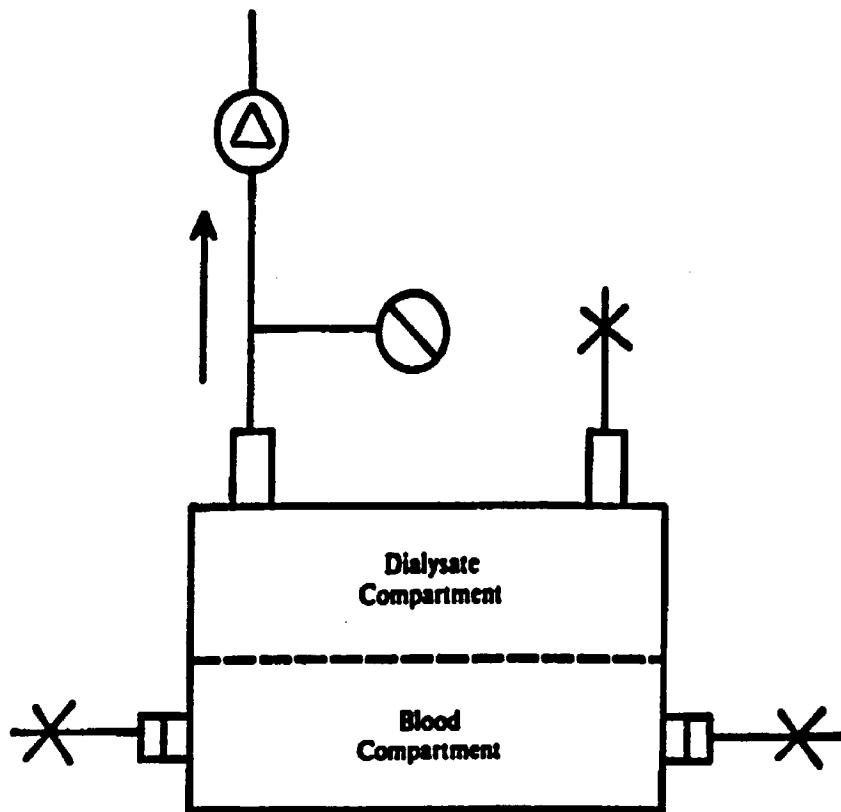


Figure 7—System for negative pressure testing

Annex A (Informative)

Rationale for the development and provisions of this standard

A.1 Introduction

This standard addresses hemodialyzer devices that are manufactured ready-to-use. Blood tubings for connecting the hemodialyzer to the blood access device(s) of the patient are not included because of the unique characteristics of these devices and differences in labeling and packaging (ANSI/AAMI RD17-1994 addresses blood tubing for hemodialysis). Dialyzers that are assembled by the user from component parts are also excluded because of the unique features of these devices, different labeling requirements, and the role of the user in establishing the performance characteristics of the device.

The products addressed by this standard include hemodialyzers as defined in sections 1 and 2 (see Scope and Normative References, respectively). Hemodialyzers are classified for regulatory purposes as Class II or Class III, which means, in keeping with the Medical Device Amendments of 1976 to the U.S. Food, Drug, and Cosmetic Act, that some of these devices eventually may be subject to the requirements of a performance standard promulgated in accordance with Section 514 of the amended act. A device is placed in Class II if the FDA deems that general controls alone are insufficient to provide reasonable assurance of its safety and effectiveness and, further, that there is enough information to establish a performance standard to provide such assurance.

The major distinction between Class II and Class III semipermeable membrane devices for treating the blood, such as a hemodialyzer, concerns the hydraulic permeability of the membrane. The AAMI Renal Disease and Detoxification Committee was unable to establish a definition in terms of this parameter, since tolerance of ultrafiltration is partly determined by the characteristics of the patient and since FDA ultimately makes this determination. Hemodialyzers operated with optional automated hemofiltration controllers for conventional hemodialysis are, however, covered by this standard. The committee believes that the FDA definition of "high

permeability" is obsolete and should be reconsidered. This is supported by the wide use of dialyzers known as high-flux dialyzers that have permeability above that level and are accepted as are other hemodialyzers (see Definitions section).

The need for a hemodialyzer standard was recognized by the AAMI committee in 1969. Efforts to develop the standard were deferred while the National Institutes of Health report, "Evaluation of Hemodialyzers and Membranes" (NIH 1977) and an FDA contract study, "Investigation of the Risks and Hazards Associated with Hemodialysis Devices" (Keshaviah et al., 1980), were being prepared. In 1980, the FDA's Gastroenterology-Urology Advisory Panel recommended the establishment of a performance standard for hemodialyzers as a high priority. The AAMI standard is the culmination of efforts by the committee to develop such a standard, based on the data developed in the NIH and FDA studies, among other sources. Many advances in technology and practice have followed, and the standard came under review for revision in 1992. This 1995 revision is the result of that review and takes into consideration developments reported through the end of 1994.

A.2 Need for the standard

Hemodialyzers are incorporated into the patient's bloodstream to supplement kidney function. A faulty device or improper operation of the device may cause serious adverse effects, such as hemorrhage, low blood pressure, infection, or illness due to inadequate treatment (uremia). The AAMI committee determined that a voluntary standard was needed to promote adequate labeling of these devices, uniformity of testing and reporting of device performance characteristics, and acceptable safety and performance of these devices. In addition, as described in A.1, the FDA has classified hemodialyzers as Class II or Class III devices.

This standard is intended to be used by manufacturers to assure the safety and the effectiveness of these devices.

While the committee was chiefly concerned with ensuring the adequate, safe treatment of the patient, additional considerations did influence the selection of the requirements. The cost of treating end-stage renal disease (ESRD) was 1.6 billion dollars in 1981, which does not include the approximately 10% of costs covered by sources other than Medicare. This cost continues to rise, despite decreased Medicare reimbursements per procedure, because more patients are being maintained by hemodialysis.

The committee has attempted to establish requirements that are consistent, whenever possible, with financial constraints and user convenience. Specific requirements have been set whenever the committee could identify a clear need for the requirement and could define a feasible test. Requirements of a more general nature or for disclosure or reporting were written when the need for a requirement was unclear, adequate performance criteria could not be defined, or an appropriate test was not available.

A.3 Rationale for the specific provisions of this standard

This section contains the rationale for each of the requirements of section 4 of the standard. The paragraph numbers below correspond to those of section 4, except for the first digit. The pressure drop across the dialyzer varies substantially among dialyzer designs. Devices with high pressure drops have been used successfully in a large number of patients for many years. Therefore, a requirement for measurement of pressure drop is no longer specified.

A.3.1 Labeling and documentation requirements

As of this writing, the federal regulation that controls the label content of a medical device is Normative Reference 2.5, which establishes requirements for proper handling, legibility, and other aspects of labeling with respect to good manufacturing practices including what constitutes mislabeling and misbranding. All labeling pertaining to hemodialyzers is controlled by this regulation and must comply with it. While this standard reiterates some of these federal labeling requirements, it also sets forth additional significant labeling criteria, specific to hemodialyzers, which the committee considered necessary to assure proper use of the device.

Section 4.1 of the standard is divided into requirements for information that should be displayed on the device itself, for information that should be provided on the shipping package, and for information that may accompany the device in separate literature when it would be impractical or superfluous to do so on the device or in the package. The information to be disclosed on the device or shipping package has been limited to minimal identifying data and to important warnings, in recognition of the limited space available on the label. It is also recognized that information is often given in several languages. Consequently, the committee decided to require that the device itself need only display identifying information, and that recommended operating conditions (except ultrafiltration control requirements) be described in the package insert/instructions for use, rather than on the shipping container.

Methods of reuse of the hemodialyzer have not been addressed in this standard, but are covered in other documents. This position is consistent with the FDA Compliance Policy Guide 7124.6, issued 1 July 1981, which concludes that "the institution or practitioner who reuses a disposable medical device should be able to demonstrate: (1) that the device can be adequately cleaned and sterilized, (2) that the physical characteristics or quality of the device will not be adversely affected, and (3) that the device remains safe and effective for its intended use." This has changed with relabeling requirements through which the manufacturer must demonstrate performance after reprocessing. Changes in this guidance are in progress; performance requirements of dialyzers remain as stated here. Reassessment of performance characteristics, sterility, and nonpyrogenicity after reprocessing for reuse are addressed in ANSI/AAMI RD47-1993, *Reuse of Hemodialyzers*.

The requirement for identifying markings to distinguish the device from similar devices was established in the absence of a consensus on a more specific method. In view of the lack of data supporting one method over another, the committee decided to defer to the discretion of the manufacturer.

The requirement for identifying blood inlet and outlet ports and dialysate inlet and outlet ports reflects the fact that optimal performance of hemodialyzers may require a specific direction of blood flow relative to dialysate flow. In particular, countercurrent flow yields a higher hemodialyzer clearance than concurrent flow. Thus, the committee felt that these ports should be identified even when the choice as to which end is the inlet and which the outlet is arbitrary.

The committee considered requiring an expiration date but determined that there are insufficient data to support its establishment. At the outset, the committee felt that some information on the time of sterilization should appear in plain language on the device to facilitate inventory control by the user and to prevent inadvertent use of hemodialyzers considered by the user to be unacceptably "old." The committee then heard arguments against displaying the month and year of sterilization; there was some concern that requiring the date of sterilization could result in considerable additional expense.

Therefore, it was tentatively decided that only the month and year of manufacture need be disclosed, for the following reasons. This date is encoded in the lot number that federal regulations require to be displayed on the device, the shipping package, and the shipping container. Changing the lot number so that the date of manufacture appears in plain language is less expensive than providing the date of sterilization. Moreover, the date of manufacture is almost always within 3 months of the date of sterilization. A discrepancy between the date of manufacture and the date of sterilization will decrease the risk of using a hemodialyzer that the user would consider unacceptably "old."

The committee finally decided to restore the requirement for disclosure of sterilization date, because most European countries require this information and thus this requirement is already being met for foreign markets. In addition, month and year of sterilization is a labeling requirement in the International Organization for Standardization proposed document, *Extracorporeal blood circuits for haemodialyzers, haemofilters and haemoconcentrators* (ISO 8638). The date of sterilization is required for the device markings only if the blood pathway is sterile outside the shipping container to avoid confusion about the sterility of a device for which the shipping container maintains the sterility of the blood pathway. Consideration was given to deleting the

requirements for disclosure on the shipping container label of a warning about the need to rinse the device before use; recommended operating conditions; and other descriptive information, warnings, and precautions. In view of the space limitations of the shipping container, the committee was persuaded to confine disclosure of operating conditions to disclosure of whether or not an ultrafiltration control machine is required. The committee decided, however, that the other information should be displayed on the shipping package, in recognition of the limited medical background of some operators, especially home dialysis patients.

The requirement that the manufacturer explain the rationale for rinsing the hemodialyzer (4.1.3(a)(2)) originates in concern that the importance of this procedure has been misunderstood. Some users have regarded the rinsing procedure only as a method for removing air from the dialyzer. Quite the contrary, the rinsing procedure is designed to remove undesirable materials from the hemodialyzer, such as residual sterilants, particulates, and Limulus lysate reactive materials. The committee considered describing such substances as "toxic," but decided to characterize them as "potentially hazardous" instead, because the adverse effects of substances removed by rinsing are still unknown.

The volume of the dialysate compartment was initially to be disclosed, since it would be useful for determining the washout time when collecting samples of ultrafiltrate for chemical analysis in lieu of blood sampling. The committee agreed, however, with opponents of such requirement: this information has little clinical relevance at the present time and does not affect the safety or efficacy of the device. Accordingly, the requirement was deleted.

The list of known adverse reactions is limited to the specific device or its materials of construction, because some adverse reactions occur only with the use of certain generic materials and it would be inappropriate to require the manufacturer to enumerate such reactions for devices that do not contain these generic materials.

Section 4.1.3(1) specifies the minimum measurements and conditions of test necessary for the user to compare one hemodialyzer type with another and to select the clinical applications of the device. At first, the committee rejected a suggestion that the limits of the conditions be those published in the manufacturer's product literature, but changed its position because innovations could render such a requirement obsolete. A requirement that clearances be measured at a blood flow rate of 200 ml/min and a dialysate flow rate of 500 ml/min was retained, because these conditions are widely used to compare hemodialyzers although practice now uses higher blood flows and sometimes higher dialysate flows.

Including TMP as a variable in 4.1.3(1)(4) is required because this factor may influence the result due to distension or contraction of the hemodialyzer membrane with pressure changes. The qualifying phrase "if appropriate" acknowledges that the membranes of some hemodialyzers (e.g., hollow fiber) are not significantly affected by pressure. The committee considered requiring disclosure of obligatory ultrafiltration rate, since attempts to achieve a zero ultrafiltration rate with equipment that rigidly controls ultrafiltration may lead to a positive dialysate-to-blood pressure gradient if the oncotic pressure of the blood is insufficient to offset the hydrostatic pressure at minimal blood-to-dialysate pressure gradients. A positive dialysate-to-blood pressure gradient is undesirable, because in the event of a membrane rupture nonsterile dialysate may be infused into the blood stream. However, the committee recognizes that localized positive dialysate-to-blood pressure gradients may be unavoidable in some dialyzers containing membranes with high hydraulic permeabilities. This condition can arise, even with moderate net ultrafiltration, if the dialysate inflow pressure must exceed the blood outflow pressure in order to achieve the required average TMP. Because there will be localized flow of fluid from dialysate to the blood stream (so-called "back-filtration") under these circumstances, users may wish to set a lower limit for microbial contaminants in the dialysate than those allowed in the Standard for Hemodialysis Systems (ANSI/AAMI RD5-1992). In certain devices, the membrane can collapse if the dialysate compartment pressure exceeds the blood compartment pressure, resulting in obstruction of the blood path; this, in turn, can lead to a higher ultrafiltration rate and, if attempts to achieve a zero ultrafiltration rate are pursued, to a pressure high enough to rupture the hemodialyzer blood tubing. The committee decided that a test for obligatory ultrafiltration would be expensive: not only pressure but also perfusate oncotic pressure and hematocrit would need to be varied. The results of such a test would be difficult to interpret because of individual variation.

Therefore, a warning is required, whenever appropriate, that attempts to achieve a zero ultrafiltration rate can cause dangerous conditions.

The standard requires disclosure of the generic materials that will come into contact with blood, to aid the user in assessing the safety of the device.

Disclosure of known incompatibilities with commonly used chemicals is required to minimize the possibility of damage to the device (e.g., alcohol degrades certain plastics).

Any information that need only be made available upon request (4.1.3(o)) is not critical to the safe, effective use of the device; requiring such information to be provided in the product literature would add unnecessarily to the cost of the product. Although the committee did recognize the potential importance of particulates emitted by the device, a requirement for particulate emission could not be set due to lack of data on particulate toxicity as well as a standard test. A proposal that these data and the results of toxicological tests need not even be made available upon request was rejected in favor of making this information available to the user, that is, the medical professional in charge of dialysis.

A maximum allowable leak rate was first specified in the standard as a performance requirement. The committee judged that data associated with leak rates are not scientifically reliable. Leak rates are generally quite low and have ceased to be a major problem. Competition in the hemodialyzer market helps assure that they will remain so.

In conclusion, it should be noted that in recommending the labeling criteria of 4.1, the committee recognized that the user has the ultimate responsibility for prudent application of the device within the constraints of the manufacturer's labeling.

A.3.2 Performance requirements

In vitro tests were chosen since *in vivo* tests, including clinical trials, are subject to a number of variables that cloud comparisons among dialyzers. Ultimately, *in vivo* tests must be interpreted by the physician, and a standard cannot be established with clinical data at the present time. *In vitro* data, on the other hand, can be standardized. Moreover, such data are valuable in making clinical decisions about hemodialyzers.

This standard not only requires disclosure of *in vitro* data but also requires disclosure of how these relate to clinical results (4.1.3(l)).

A.3.2.1 Ultrafiltration coefficient

Control of variability of ultrafiltration coefficients is necessary to prevent excessive or inadequate removal of fluid from the patient during dialysis. While the committee supported the contention that, ideally, the variability should be less than $\pm 10\%$ (Keshaviah et al., 1980), the current state of the art does not permit this degree of accuracy. The variability reported by a major supplier of Cuprophane membranes is $\pm 17\%$. Other manufacturers report similar values for the variability of the manufactured membrane, irrespective of its composition. Although tighter performance characteristics were thought desirable, the committee accepted $\pm 17\%$ state-of-the-art and $\pm 20\%$ as the requirement (4.1.3[l][1]). The committee requests that the manufacturer report the details of testing including number of samples and statistical analysis. If some manufacturer is able to produce a membrane of greater consistency, that fact will add to its appeal and assist in advancing production technique. Variability is further widened by differences in the surface area of the device.

A.3.2.2 Solute clearance

Exchange of solutes through the membrane is the second function of hemodialyzers and accounts for much of the effect of hemodialysis. Variations in solute clearance between lots of membrane and of manufactured hemodialyzers are difficult to control with present technology. Manufacturers are unwilling to specify an allowable range of variation for transfer of all solutes. The range of variation usually seen is of a magnitude that does not constitute an immediate threat to patients, and results of solute transfer are routinely monitored by

clinicians, so that adjustments in treatments can be made to cope with changes in solute clearance; thus the committee was able to accept the lack of a standard for variation, for the moment, of solutes other than urea. Instead, manufacturers are to disclose qualifying tests, including number of samples and statistical analysis. Where pressure changes affect clearance, that, too must be disclosed and described. The committee accepts $\pm 10\%$ as the maximum allowable variance for urea since it does not pose a hazard to patients, but believes a tighter standard is desirable when feasible.

As solute clearance of newer, larger, dialyzers has increased, so also has convective transfer, complicating measurement of total solute transfer. Indeed, some members of the committee felt that convective transfer as indicated by KUF was sufficient to discriminate between "conventional" and "high-flux" dialyzers. That was not accepted. The committee debated at length, believing that a practical definition of high-flux was needed. Some members wanted to use transport of beta-2 microglobulin as the key differentiation. This was not accepted due to the difficulty and expense of the measurement of beta-2 microglobulin clearance, which is done as an indirect estimate, and because some members feared misleading clinicians into believing that high-flux dialyzers can make a significant difference in beta-2 retention, which is not supported by current data. A method for estimating beta-2 microglobulin removal is included for reference.

Although the utility of measurements of clearance of creatinine and vitamin B₁₂ were acknowledged to be of no direct clinical relevance, the majority of the committee was unwilling to remove these measurements from the standard. Manufacturers noted that customers expect to see these values, so they will have to produce them.

The committee acknowledges the need for development of indicator solutes of molecular weight and behavior similar to beta-2 microglobulin which are economical and capable of accurate measurement for *in vitro* use. The suggestion of cytochrome C as such a solute brought forth reports of uneven adsorption on various membranes and inconsistent clearance measurement, thus it was not presently acceptable. This issue will continue to be studied by the committee.

A.3.2.3 Blood compartment volume and compliance

Since the blood of the patient is generally diluted by the fluid in the hemodialyzer at the beginning of dialysis, the volume of the blood compartment is an important parameter in selecting hemodialyzers. This remains a matter of medical judgment, however, since the effect of the hemodialyzer has to do with not only the blood volume of the patient but also less well-defined clinical variables. Therefore, blood compartment volume has not been specified in this standard. The variability of the blood volume during dialysis is a function of the distensibility of the membrane, but this factor has become relatively insignificant because of the small priming volumes of current hemodialyzers and the noncompliance of hollow fiber dialyzers.

There *is* a requirement for when the measurement of volume is made. Changes in the blood compartment volume can also affect the performance of the dialyzer by changing the width of the blood stream and the dialysate stream. The committee considered prohibiting an adverse effect of increasing blood volume on ultrafiltration rate, but decided not to because this phenomenon is inherent to some dialyzers. Instead, a disclosure statement is required, when appropriate.

A.3.3 Mechanical/structural integrity requirements

A.3.3.1 General structural integrity

The committee felt that the dialyzer should withstand a pressure higher than the maximum operating pressure, as a safety factor against leaks. An arbitrary standard of 2.0 times the maximum operating pressure was first suggested. This value exceeds the 1.5-fold increase recommended by the ISO committee, and the ISO standard was accepted for positive pressure tests, because it has been widely used without evidence of dialyzer malfunction attributable to defects in mechanical integrity. A maximum negative pressure of 700 mmHg was selected for negative pressure tests, since this is the most negative pressure that can be readily achieved with the test system. The blood tubing connections can be included in the test, since they are standardized (4.5.1).

A.3.3.2 Membrane integrity

Membrane leaks occur regularly despite optimal quality control procedures of membrane manufacturers. Therefore, a test for membrane integrity on each dialyzer is required. This test is less stringent than the mechanical integrity test, since the goal is to minimize blood leaks during dialysis rather than to assure initial qualification of the entire assembly.

Initially, the proposed requirement coincided with that of the proposed ISO standard--that is, a method capable of detecting a potential blood leak of 0.35 ml/min at a hematocrit of 25% (0.25)--the rationale being that such sensitivity is required for the hemodialysis system blood leak detector. Subsequently, however, the committee concluded that this requirement was too specific and therefore declined to define a specific blood leak rate. Instead, it is required that there be no evidence of blood leak when the device is tested according to 5.3.2.

A.3.3.3 Package integrity

This requirement is necessary because of the stresses to which a dialyzer may be subjected during shipment.

A.3.4 Device cleanliness/requirements for materials

A.3.4.1 Sterility and nonpyrogenicity

No specific tests for sterility assurance are specified since each manufacturer is required by the FDA to comply with GMP as they apply to sterility claims. Compliance with these regulations involves appropriate process qualification and controls, appropriate use of biological indicators, and final product sterility testing (or parametric release, as approved by FDA for each manufacturer). Therefore, it is not practical to specify a particular test for determining sterility, since the nature of this microbiological contamination is such that a test can only expose a heavy contamination level.

The release of a product labeled nonpyrogenic normally entails testing each batch of product for pyrogenicity, using either the USP Rabbit Test or the alternate Limulus Amebocyte Lysate (LAL) Test; however, parametric release is also an alternative, provided that approval is received from FDA. The USP Rabbit Test and the LAL Test are considered tests for nonpyrogenicity. Tests for sterilization and pyrogenicity are not required for the dialysate compartment, since experience abundantly demonstrates the safety of devices that have not undergone sterility and pyrogenicity testing of the dialysate compartment. Further, a requirement for such tests increases costs.

A.3.4.2 Material Safety

This requirement is necessary to exclude materials that can cause adverse effects when incorporated into the bloodstream.

A.3.4.3 Residual ethylene oxide

Ethylene oxide and residues of its reaction products, which can remain in a dialyzer after sterilization, are potentially toxic. The proposed FDA regulation limiting maximum residual ethylene oxide and residual ethylene chlorohydrin and ethylene glycol is accepted by the committee without additions or modifications.

A.3.5 Tubing connectors

Inadequate connections with the tubing connecting the device to the patient blood access device can cause hemorrhage or air embolism. ISO 8637 specifies the configuration of both blood and dialysate line connectors to assure compatibility and secure fit.

A.4 Tests

At first, more technical details were specified in the tests section. This approach was widely criticized, and the proposed section was replaced by a general one listing many requirements in performance terms and organized

according to section 4, with the caveat that a different test sequence may be followed if the results are not significantly affected.

The allowed temperature variability of $\pm 1.5^\circ \text{C}$ is the same as that specified in the American National Standard, Hemodialysis Systems. A specific test for membrane integrity is not described for the reasons given in A.3.3.2. Aqueous solutions had been specified, but this was changed for several tests, because a solution with the viscosity of blood is required for meaningful results (see A.4.2.3). In tests requiring aqueous solutions, dialysate was specified, because it resembles the ionic strength of blood and it is thought that ionic strength may have an effect on clearance results.

A.4.2.1 Ultrafiltration coefficient

Initially, a test was proposed that involved using a closed-loop system and timing the fall of the volume in the patient reservoir. While in the past this test was more convenient for dialyzers designed for recirculation systems having an open dialysate compartment, the direct method now proposed is more accurate (Keshaviah et al., 1982).

A.4.2.2 Solute clearance

A closed-loop method for maintaining the level in the "patient" reservoir by infusing solution from another reservoir was rejected in favor of a test starting with enough volume in the "patient" reservoir so that it will not be emptied by ultrafiltration during the test, and then correcting for the ultrafiltration effect mathematically. This method gives more accurate results than does the practice of replacing ultrafiltered solution with another solution added to the system, since ultrafiltered fluid carries solute with it by convection. The definition of the volume of the closed loop is important, because the solution in the venous line is not part of the well-mixed volume that is being dialyzed.

Cytochrome C is added as a practically measurable indicator which may serve as a marker for other large molecules, such as beta-2 microglobulin. Specific correspondence of the two has not been demonstrated. Cytochrome C is also not handled in a uniform fashion by all membranes.

Methodology for cytochrome C: cytochrome C *in vitro* clearance procedure (recirculating at zero ultrafiltration).

- a) Prime dialyzer with 200 ml of the cytochrome C solution. Place outlet line into the 4-liter reservoir and recirculate at Q_{B_i} of 300 ml/min. Measure the outlet Q_{B_o} by recording the time in seconds required to collect 150 ml of solution. Pour the solution back into flask after stopping the stopwatch.
- b) Collect a 2 ml sample from the reservoir and start the stopwatch.
- c) Collect samples at 5, 10, 15, 20, and 30 min from the reservoir.
- d) Return cytochrome C solution in the dialyzer to the reservoir with saline. Read the absorbance of the samples on the visible spectrophotometer at a wavelength of 550 nm.
- e) Calculate the clearance by calculating the ratio of absorbance at zero time divided by the absorbance at the other sample times ($\ln A_0/A_t$) and taking the natural logarithm of this ratio. A linear regression of the $\ln A_0/A_t$ and sample times will determine the clearance of cytochrome C by this dialyzer. The slope of the line times the reservoir volume is the actual clearance value.

Beta-2 microglobulin clearance cannot be measured directly by standard clearance methods due to the small changes occurring in levels across the hemodialyzer and difficulty in precise measurement. It can be estimated from pre- and post-dialysis beta-2 concentration, weight change, and the best available estimate of total urea volume. Beta-2 generation is assumed to be 0 net during dialysis on the assumption that the body is in a steady state.

Beta-2 microglobulin clearance is calculated under a one-pool variable volume model, in which the post-dialysis

volume of distribution of beta-2 microglobulin is assumed to be equal to 1/3 the post-dialysis urea volume (NIH, 1995).

The equation for the clearance is as follows:

$$K_d = Q_{UF} \left[1 + \frac{\log (\beta_{2_{post}} / \beta_{2_{pre}})}{\log (V / (V + Q_{UF} \cdot t))} \right]$$

where:

K_d = clearance of beta-2;

Q_{UF} = ultrafiltration rate;

$\beta_{2_{post}}$ = post-dialysis beta-2 concentration;

$\beta_{2_{pre}}$ = pre-dialysis beta-2 concentration;

V = 1/3 the total urea volume;

t = duration of dialysis in minutes.

For vitamin B₁₂, clearance by the spectrophotometric method may be done by either the open- or closed-loop system since the B₁₂ clearance of current dialyzers is high enough to achieve accurate results either way. According to Dr. Prakash Keshaviah, the mass balance error with the closed-loop method is 3% for urea when optimal analytical technique is used, 2% for creatinine and 5% for Vitamin B₁₂ by the spectrophotometric method. Concentration of the test substances are clinically relevant for urea and creatinine, while the value specified for vitamin B₁₂ is widely accepted as appropriate.

A.4.2.3 Blood compartment volume and compliance

The 1984 version contained a procedure using kerosene because it was neither ultrafilterable nor dialyzable. Typically this yields somewhat different results than measurements made with water. Because of the prevalence of dialyzer reuse in the U.S., it was decided that aqueous measurements would be more useful to the clinician than those made with kerosene. Regardless of the method, the dialyzer should be wetted before volume measurement so the dialyzer is in its most compliant state when the volume is measured.

A.4.3 Mechanical/structural integrity

A.4.3.1 General structural integrity

A negative pressure test is specified for the dialysate compartment, because the dialysate compartment is not subjected to substantial positive pressure and because of the opinion that leaks sometimes become apparent with suction that had not been obvious under positive pressure.

A.4.3.2 Membrane integrity

A more specific test cannot be specified due to the considerations given in [A.3.3.2](#).

A.4.3.3 Package integrity

Specific tests are not available for this requirement.

A.4.4 Device cleanliness/requirements for materials

A.4.4.1 Sterility and nonpyrogenicity

These tests are required by federal regulation.

A.4.4.2 Material safety

The tests described in this section are those commonly used for purposes of evaluating toxicity. The committee considered requiring a perfusion test with aqueous and oil extracts as reagents, since some potentially toxic materials are eluted more readily by one perfusate than the other. This specific test is not used in the United States, but ISO has issued guidelines for similar ones. Therefore, the committee decided to cite the ISO guidelines (Normative References 2.10 and 2.11) as the source of test methodologies for safety evaluation.

A.4.4.3 Residual ethylene oxide

Tests for measuring residual ethylene oxide (EO) are found in the AAMI *Recommended Practice for Determining Ethylene Oxide Residuals in Medical Devices*. (Normative Reference 2.1).

Annex B (Informative)

Bibliography

KESHAVIAH, PR, LUEHMANN, DA, SHAPIRO, FL, and COMTY, C. *Investigation of the Risks and Hazards Associated with Hemodialysis Systems*. Technical report, contract #223-78-5046. Silver Spring (Md.): U.S. Depart. of Health and Human Services, Public Health Service/Food and Drug Administration/Bureau of Medical Devices, 1980.

KESHAVIAH, PR, CONSTANTINE, EG, LUEHMANN, D, and SHAPIRO, FL. Dialyzer ultrafiltration coefficient. Comparison between in vitro and in vivo values. *Artif Organs*, 1982, vol. 6, p. 23.

NATIONAL INSTITUTES OF HEALTH. *Evaluation of Hemodialyzers and Membranes*. DHEW pub no. NIH 77-1924. Bethesda (Md.): U.S. Depart. of Health, Education, and Welfare. National Institute of Arthritis, Metabolism, and Digestive Diseases, 1977.

NATIONAL INSTITUTES OF HEALTH. *National Institutes of Health HEMO Study Protocol*, 1995.

Annotations from RD16.pdf

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Annotation 1; Label: AAMI; Date: 09/28/2000 11:21:24 AM

1 Available from American National Standards Institute, 11 W. 42nd Street, New York, NY 10036.

Annotation 2; Label: AAMI; Date: 09/28/2000 11:23:16 AM

Ibid

Amendment 1 to ANSI/AAMI RD16:1996, Hemodialyzers

2 Normative references

Replace normative references 2.1 and 2.2 with the following text:

2.1 Association for the Advancement of Medical Instrumentation. *Biological evaluation of medical devices, Part 7: Ethylene oxide sterilization residuals*. ANSI/AAMI/ISO 10993-7:1995. Arlington (Vir.): AAMI, 1995. American National Standard.

4.4.3 Residual ethylene oxide

Replace the entire section with the following text:

4.4.3 Residual ethylene oxide and ethylene chlorohydrin

The limit for ethylene oxide (EO) and ethylene chlorohydrin (ECH) residuals for each hemodialysis device shall be set according to normative reference 2.1, section 4.3.2, *Prolonged exposure limit* (presently 2 mg/day and 60 mg/month), adjusted for the average number of hemodialysis procedures per month for a dialysis patient, not to exceed 5 mg per device.

5.4.3 Residual ethylene oxide

Replace the entire section with the following text:

5.4.3 Residual ethylene oxide and ethylene chlorohydrin

Methodology for determining EO and ECH residuals is included in normative reference 2.1.

A.3.4.3 Residual ethylene oxide

Replace the entire section with the following text:

A.3.4.3 Residual ethylene oxide and ethylene chlorohydrin

EO and ECH residues, which can remain in a dialyzer after sterilization, are potentially toxic.

A.4.4.3 Residual ethylene oxide

Replace the entire section with the following text:

A.4.4.3 Residual ethylene oxide and ethylene chlorohydrin

Tests for measuring residual EO and ECH are found in normative reference 2.1.

Developed by
Association for the Advancement of Medical Instrumentation

Approved 20 June 2002 by
American National Standards Institute