List of Titles

American National Standard

ANSI/AAMI RD62:2001

Water treatment equipment for hemodialysis applications

AAMI Association for the Advancement of Medical Instrumentation

The Objectives and Uses of AAMI Standards and Recommended Practices

It is most important that the objectives and potential uses of an AAMI product standard or recommended practice are clearly understood. The objectives of AAMI's technical development program derive from AAMI's overall mission: the advancement of medical instrumentation. Essential to such advancement are (1) a continued increase in the safe and effective application of current technologies to patient care, and (2) the encouragement of new technologies. It is AAMI's view that standards and recommended practices can contribute significantly to the advancement of medical instrumentation, provided that they are drafted with attention to these objectives and provided that arbitrary and restrictive uses are avoided.

A voluntary *standard* for a *medical device* recommends to the manufacturer the information that should be provided with or on the product, basic safety and performance criteria that should be considered in qualifying the device for clinical use, and the measurement techniques that can be used to determine whether the device conforms with the safety and performance criteria and/or to compare the performance characteristics of different products. Some standards emphasize the information that should be provided with the device, including performance characteristics, instructions for use, warnings and precautions, and other data considered important in ensuring the safe and effective use of the device in the clinical environment. Recommending the disclosure of performance characteristics often necessitates the development of specialized test methods to facilitate uniformity in reporting; reaching consensus on these tests can represent a considerable part of committee work. When a drafting committee determines that clinical concerns warrant the establishment of *minimum* safety and performance criteria, referee tests must be provided and the reasons for establishing the criteria must be documented in the rationale.

A *recommended practice* provides guidelines for the use, care, and/or processing of a medical device or system. A recommended practice does not address device performance *per se*, but rather procedures and practices that will help ensure that a device is used safely and effectively and that its performance will be maintained.

Although a device standard is primarily directed to the manufacturer, it may also be of value to the potential purchaser or user of the device as a fume of reference for device evaluation. Similarly, even though a recommended practice is usually oriented towards health care professionals, it may be useful to the manufacturer in better understanding the environment in which a medical device will be used. Also, some recommended practices, while not addressing device performance criteria, provide guidelines to industrial personnel on such subjects as sterilization processing, methods of collecting data to establish safety and efficacy, human engineering, and other processing or evaluation techniques; such guidelines may be useful to health care professionals in understanding industrial practices.

In determining whether an AAMI standard or recommended practice is relevant to the specific needs of a potential user of the document, several important concepts must be recognized:

All AAMI standards and recommended practices are *voluntary* (unless, of course, they are adopted by government regulatory or procurement authorities). The application of a standard or recommended practice is solely within the discretion and professional judgment of the user of the document.

Each AAMI standard or recommended practice reflects the collective expertise of a committee of health care professionals and industrial representatives, whose work has been reviewed nationally (and sometimes internationally). As such, the consensus recommendations embodied in a standard or recommended practice are intended to respond to clinical needs and, ultimately, to help ensure patient safety. A standard or recommended practice is limited, however, in the sense that it responds generally to perceived risks and conditions that may not always be relevant to specific situations. A standard or recommended practice is an important *reference* in responsible decision-making, but it should never *replace* responsible decisionmaking.

Despite periodic review and revision (at least once every five years), a standard or recommended practice is necessarily a static document applied to a dynamic technology. Therefore, a standards user must carefully review the reasons why the document was initially developed and the specific rationale for each of its provisions. This review will reveal whether the document remains relevant to the specific needs of the user.

Particular care should be taken in applying a product standard to existing devices and equipment, and in applying a recommended practice to current procedures and practices. While observed or potential risks with existing equipment typically form the basis for the safety and performance criteria defined in a standard, professional judgment must be used in applying these criteria to existing equipment. No single source of information will serve to identify a particular product as "unsafe". A voluntary standard can be used as one resource, but the ultimate decision as to product safety and efficacy must take into account the specifics of its utilization and, of course, cost-benefit considerations. Similarly, a recommended practice should be analyzed in the context of the specific needs and resources of the individual institution or firm. Again, the rationale accompanying each AAMI standard and recommended practice is an excellent guide to the reasoning and data underlying its provision.

In summary, a standard or recommended practice is truly useful only when it is used in conjunction with other sources of information and policy guidance and in the context of professional experience and judgment.

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American National Standard

ANSI/AAMI RD62:2001
(Partial revision of ANSI/AAMI RD5:1992)

Water treatment equipment for hemodialysis applications

Developed by
Association for the Advancement of Medical Instrumentation

Approved 6 August 2001 by
American National Standards Institute, Inc.

Abstract: This American National Standard addresses devices used to treat water intended for use in the delivery of hemodialysis. Included in the scope of the standard is water used for (1) the preparation of concentrates from powder at a dialysis facility, (2) the preparation of dialysate, and (3) the reprocessing of dialyzers for multiple use.

Keywords: dialysis, water quality, concentrates, dialyzing fluids, medical equipment, reuse

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AAMI Standard

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Committee representation

Association for the Advancement of Medical Instrumentation
AAMI Renal Disease and Detoxification Committee

This standard was developed by the AAMI Water for Hemodialysis Task Group under the auspices of the AAMI Renal Disease and Detoxification Committee. Committee approval of the standard does not necessarily imply that all committee members voted for its approval.

At the time this document was published, the **AAMI Renal Disease and Detoxification Committee** had the following members:

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

Foreword

This voluntary standard was developed by the AAMI Renal Disease and Detoxification Committee.

The American National Standard *Hemodialysis systems* was first approved in May 1982 and was published under the designation ANSI/AAMI RD5:1981. In 1996, during the five-year review of RD5, the AAMI Renal Disease and Detoxification Committee determined that the hemodialysis community would be better served by this standard if it were divided into three parts: (1) hemodialysis concentrates, (2) water, and (3) equipment. ANSI/AAMI RD62:2001, *Water treatment equipment for hemodialysis applications*, represents the work done by the AAMI Water for Hemodialysis Working Group.

This standard reflects the conscientious efforts of concerned physicians, clinical engineers, nurses, dialysis technicians, and dialysis patients, in consultation with device manufacturers and government representatives, to develop a standard for performance levels that could be reasonably achieved at the time of publication. The term "consensus," as applied to the development of voluntary medical device standards, does not imply unanimity of opinion, but rather reflects the compromise necessary in some instances when a variety of interests must be merged.

As used within the context of this document, "shall" indicates requirements strictly to be followed in order to conform to the standard; "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 should be avoided but is not prohibited; "may" is used to indicate that a course of action is permissible within the limits of the standard; and "can" is used as a statement of possibility and capability. "Must" is used only to describe "unavoidable" situations, including those mandated by government regulation.

The concepts incorporated in this standard should not be considered inflexible or static. This standard, like any other, must be reviewed and updated periodically to assimilate progressive technological developments. To remain relevant, it must be modified as advances are made in technology and as new data come to light.

This is a voluntary standard, developed for use by manufacturers and health care professionals. The format and structure of this standard make it unsuitable for use as an enforced regulation.

Suggestions for improving this standard are invited. Comments and suggested revisions should be sent to Standards Department, AAMI, 1110 N. Glebe Rd., Suite 220, Arlington, VA 22201-4795.

American National Standard **ANSI/AAMI RD62:2001**

Water treatment equipment for hemodialysis applications

1 Scope

1.1 General

This standard covers devices used to treat water intended for use in the delivery of hemodialysis. Included in the scope of the standard is water used for: (1) the preparation of concentrates from powder at a dialysis facility, (2) the preparation of dialysate, and (3) the reprocessing of dialyzers for multiple use. The provisions of this standard apply to individual water treatment devices and to water treatment systems assembled from one or more of these devices. In the first instance, this standard is directed at the individual or company that specifies the complete water treatment system and, second, at the vendor who assembles and installs the system. Since systems may be assembled from a number of individual water treatment devices, the provisions of this standard are also directed at the manufacturers of these devices, provided that the manufacturer indicates that the device is intended for use in hemodialysis applications. This standard is written principally to address water treatment systems for dialysis facilities treating multiple patients. However, many of its provisions equally apply to water treatment systems used in applications where a single patient may be treated, such as in a home dialysis or acute hospital dialysis setting. Specifically, requirements for the chemical and microbiological quality of water are considered to apply in all settings, regardless of whether a single patient or many patients are being treated.

The physician in charge of dialysis has the ultimate responsibility for selecting a water treatment system and maintaining the performance of that system once it has been installed and its performance has been verified.

The requirements established by this standard will help protect hemodialysis patients from adverse effects arising from known chemical and microbial contaminants found in water supplies. However, proper dialysis and patient safety is ultimately dependent on the quality of the dialysate. Since the manufacturer of water treatment equipment does not have control over the dialysate, any reference to dialysate in this standard is for clarification only and not a requirement of the manufacturer. The responsibility for assuring that the dialysate is not contaminated, mismatched, or otherwise damaging to the patient rests with the clinical professionals caring for the patient under the supervision of the medical director.

1.2 Inclusions

The scope of this standard includes all devices, piping, and fittings between the point at which potable water is delivered to the water purification system and the point of use of the purified water. Examples of components included within the scope of this standard are water purification devices, on-line water quality monitors (such as conductivity monitors), and piping systems for the distribution of purified water.

1.3 Exclusions

Excluded from the scope of this standard are dialysate supply systems that proportion water and concentrates to produce dialysate, sorbent dialysate regeneration systems that regenerate and recirculate small volumes of the dialysate, dialysate concentrates, hemodiafiltration systems, hemofiltration systems, systems that process dialyzers for multiple use, and peritoneal dialysis systems. Some of these devices, such as dialysate supply systems and concentrates, are addressed in other American National Standards. Also excluded from the scope of this standard are requirements for the ongoing monitoring of the purity of water used for dialysate, concentrate preparation, or dialyzer reprocessing.

NOTE—For an explanation of the need for this standard and the rationale for its specific provisions, see annex A.

2 Normative references

2.1 U.S. FOOD AND DRUG ADMINISTRATION. *Guidance for the Content of Premarket Notifications for Water Purification Components and Systems for Hemodialysis*. Rockville, MD: U.S. Food and Drug Administration, 1997. <http://www.fda.gov/cdrh/ode/hemodial.pdf>

2.2 ASSOCIATION FOR THE ADVANCEMENT OF MEDICAL INSTRUMENTATION. *Hemodialysis Systems* (ANSI/AAMI RD5:1992). American National Standard. Arlington (Vir.): AAMI, 1992.

2.3 AMERICAN PUBLIC HEALTH ASSOCIATION. *Standard Methods for the Examination of Water and Wastewater,* 19th ed. Washington, DC: APHA, 1995.

2.4 U.S. ENVIRONMENTAL PROTECTION AGENCY. *Methods for the Determination of Metals in Environmental Samples, Supplement 1* (EPA-600-R-94-111). Cincinnati (Ohio): Environmental Monitoring Systems Laboratory, 1994. <http://www.epa.gov/OGWDW/methods/methods.html>

2.5 THE UNITED STATES PHARMACOPEIAL CONVENTION, INC. *United States Pharmacopeia XXIII*. Easton (Pa.): Mack Publishing, 1994.

2.6 U.S. ENVIRONMENTAL PROTECTION AGENCY. *Safe Drinking Water Act, 1996* (Public law 104-182). Washington, DC: EPA, 1996.

[See also *National Primary and Secondary Drinking Water Regulations*. U.S. Environmental Protection Agency, Office of Ground Water and Drinking Water. <http://www.epa.gov/OGWDW/creg.html>]

3 Terms and definitions

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

3.1 action level: The concentration of a contaminant at which steps should be taken to interrupt the trend toward higher, unacceptable levels.

3.2 bacteriology: The area of study within the field of microbiology that deals with the study of bacteria.

3.3 chlorine, combined: Chlorine that is chemically combined, such as in chloramine compounds. No direct test exists for measuring combined chlorine, but it can be measured indirectly by measuring both total and free chlorine and calculating the difference.

3.4 chlorine, free: Dissolved molecular chlorine.

3.5 device: An individual water purification unit, such as a softener, carbon adsorption bed, reverse osmosis unit, or deionizer. This term is synonymous with the term “component” as used by the U.S. Food and Drug Administration in its *Guidance for the Content of Premarket Notifications for Water Purification Components and Systems for Hemodialysis* (see 2.1).

3.6 dialysate: An aqueous fluid containing electrolytes and usually dextrose, which is intended to exchange solutes with blood during hemodialysis. The word “dialysate” is used throughout this document to mean the fluid made from water and concentrate that is delivered to the dialyzer by the dialysate supply system. Such phrases as “dialyzing fluid” or “dialysis solution” may be used in place of dialysate. It does not include peritoneal dialysis fluid.

3.7 dialysate supply system: Devices that prepare dialysate on line from water and concentrate or store and distribute premixed dialysate; circulate the dialysate through the dialyzer; monitor the dialysate for temperature, conductivity, pressure, flow, and blood leaks; and prevent dialysis during disinfection or cleaning modes. The term includes reservoirs; conduits; proportioning devices for the dialysate; and monitors, associated alarms, and controls assembled as a system for the characteristics listed above. The dialysate supply system is often an integral part of single-patient dialysis machines (see 2.2).

3.8 disinfection: The destruction of pathogenic and other kinds of microorganisms by thermal or chemical means. Disinfection is a less lethal process than sterilization, since it destroys most recognized pathogenic microorganisms, but not necessarily all microbial forms. This definition of disinfection is equivalent to low-level disinfection in the Spalding classification.

3.9 empty bed contact time: The empty bed contact time (EBCT) is a measure of how much contact occurs between particles, such as activated carbon, and water as the water flows through a bed of the particles. EBCT (minutes) is calculated from the following equation:

$$EBCT = (7.48 \times V)/Q$$

where V is the volume of particles in the bed (ft^3) and Q is the flow rate of water through the bed (gal/min).

3.10 endotoxin: Endotoxins are the major component of the outer cell wall of gram-negative bacteria. Endotoxins are lipopolysaccharides, consisting of a polysaccharide chain covalently bound to lipid A. Endotoxins can acutely activate both humoral and cellular host defenses, leading to a syndrome characterized by fever, shaking chills, hypotension, multiple organ failure, and even death if allowed to enter the circulation in a sufficient dose. Long-term

exposure to low levels of endotoxin has been implicated in a chronic inflammatory response, which may contribute to some of the long-term complications seen in hemodialysis. However, the mechanisms of this process remain incompletely understood. (See also pyrogen.)

3.11 EU: Endotoxin units as assayed by the *Limulus* Amebocyte Lysate (LAL) method when testing for endotoxins. Because endotoxins differ in their activity on a mass basis, their activity is referred to a standard *E. coli* endotoxin. The current standard (EC-6) is prepared from *E. coli* O:113:H10. The relationship between mass of endotoxin and its activity varies with both the lot of LAL and the lot of control standard endotoxin being used. Since standards for endotoxin were harmonized in 1983 with the introduction of EC-5, the relationship between mass and activity of endotoxin has been approximately 10 EU/ng.

3.12 feed water: Water supplied to a water treatment system or individual component thereof.

3.13 germicide: An agent that kills microorganisms.

3.14 hemodiafiltration: Hemodiafiltration is a form of renal replacement therapy in which waste solutes are removed from blood by a combination of diffusion and convection through a high-flux membrane. Diffusive solute removal is achieved using a dialysate stream as in hemodialysis. Convective solute removal is achieved by adding ultrafiltration in excess of that needed to obtain the desired weight loss; fluid balance is maintained by infusing a sterile, pyrogen-free replacement solution into the blood either before (pre-dilution hemodiafiltration) or after (post-dilution hemodiafiltration) the dialyzer.

3.15 hemofiltration: Hemofiltration is a form of renal replacement therapy in which waste solutes are removed from blood by convection. Convective transport is achieved by ultrafiltration through a high-flux membrane. Fluid balance is maintained by infusing a sterile, pyrogen-free replacement solution into the blood either before (pre-dilution hemofiltration) or after (post-dilution hemofiltration) the hemofilter. (Note that there is no dialysate stream in hemofiltration.)

3.16 manufacturer: The bearer of the responsibilities addressed to the “manufacturer” in this standard. Under this definition, “manufacturer” includes in the first instance the individual or company that specifies or designs a water treatment system. The “manufacturer” may also include the vendor that installs or is responsible for installing a water treatment system, as well as the primary manufacturer of a device or system as indicated on the label of the device or system if that manufacturer has indicated that it is intended for hemodialysis applications.

3.17 microbial: Term referring to microscopic organisms, bacteria, fungi, etc. (See also bacteriology.)

3.18 microfilter: A filter designed to remove particles in the range 0.1 to 3 microns in diameter. Microfilters have an absolute size cut-off and are available in both dead-end and cross-flow configurations.

3.19 nonpyrogenic: Providing a burden of ≤ 5 EU/kg body weight/h of bacterial endotoxin as determined by the *Limulus* Amebocyte Lysate (LAL) assay or equivalent within the level of error of test methods for such determinations, and maintained in that state by suitable means. With respect to liquid dialysate concentrates, an endotoxin concentration ≤ 5 EU/mL traditionally has been considered to be nonpyrogenic.

3.20 product water: Water produced by a water treatment system or individual component thereof.

3.21 proportioning system: Apparatus that proportions water and hemodialysis concentrate to prepare dialysate.

3.22 pyrogen: Fever-producing substance. Note that pyrogens are most often lipopolysaccharides of gram-negative bacterial origin. (See also endotoxin.)

3.23 sorbent regeneration system: A system that regenerates dialysate by passing the dialysate through substances that restore the dialysate to a condition comparable to fresh dialysate.

3.24 total dissolved solids (TDS): The sum of all ions in a solution, often approximated by means of electrical conductivity or resistivity measurements. TDS measurements are commonly used to assess the performance of reverse osmosis units. TDS values are often expressed in terms of $CaCO_3$ or NaCl equivalents (ppm).

3.25 ultrafilter: A membrane filter with a pore size in the range 0.001 to 0.05 μm. Performance is usually rated in terms of a nominal molecular weight cut-off (MWCO), which is defined as the smallest molecular weight species for which the filter membrane has more than 90 % rejection. Depending on their nominal MWCO, ultrafilters may be used to remove particles and solutes as small as 1000 dalton in size. Ultrafilters with a nominal MWCO of 20,000 or less are generally adequate for endotoxin removal. Ultrafilters are usually configured in a cross-flow mode. Note that some ultrafilters also remove endotoxins by adsorption.

3.26 USP: *United States Pharmacopeia*, the current version of this official compendium (see 2.5).

3.27 user: This medical device standard is directed to the manufacturer of the device, and in that context the "user" is the physician or his or her representative.

3.28 water treatment system: A collection of water purification devices and associated piping, pumps, valves, gauges, etc., that together produce purified water for hemodialysis applications and deliver it to the point of use. (See also device.)

4 Requirements

4.1 Labeling and documentation requirements

NOTE—The term "labeling," as used in this standard, includes any written material accompanying any water treatment device or system, such as instructions for use and operator's manuals, or any instructions or control feature markings attached to the device or system.

4.1.1 Device markings

The following information shall accompany each water treatment device or system. Items 1 through 3 shall be directly affixed to the device or system or, in the case of disposable elements, to the immediate packaging, whereas items 4 through 6 may be provided in accompanying product literature.

1. Name and address of manufacturer.
2. Trade name and type of device.
3. Model and serial number.
4. A warning that product literature should be read before use (if appropriate).
5. Prominent warnings about substances (e.g., germicides) that must be removed from the device before using the product water for dialysis.
6. Identification of fitting type or specification when necessary to prevent improper connections.

4.1.2 Product literature

The manufacturer shall provide literature to each user that contains, but is not necessarily limited to, the following information:

1. Warnings that selection of water treatment equipment for dialysis is the responsibility of the dialysis physician and that product water should be tested periodically (see 5.2).
2. A description of the device or system, including a list of monitors, alarms, and component devices provided as standard equipment.
3. A schematic diagram of the device or system showing the location of any valves, on-line monitors, or sampling ports.
4. Operating specifications, such as maximum and minimum input water temperature, pressure and flow rate, limits on input water quality, pressure of product water at various flow rates, and maximum output of product water.
5. Detailed instructions for use, including initial start-up; testing and calibration; operation and meaning of alarms; operational adjustments to monitors, alarms, and controls; and connections to other equipment.
6. An explicit statement of the relationship between feed water quality and product water quality for the chemical contaminants listed in Table 1, bacteria, and endotoxins.
7. For systems, the minimum quality of feed water required for the system to produce product water meeting the chemical requirements of this standard.
8. For systems, a warning that although a water treatment system may produce water of sufficient quality to meet the requirements of this standard, distribution of the water may degrade its quality to the point where it no longer meets the requirements of the standard if the distribution system is not maintained appropriately.
9. Safety features and warnings concerning the consequences if these features are circumvented.
10. Information pertaining to on-line monitors of water quality, including operational factors that may affect monitor performance (e.g., temperature).

11. In the case of systems whose product water is proportionally related to feed water quality, warnings that feed water quality must be monitored. Since changes in product water may exceed acceptable limits if feed water deteriorates significantly, the user is responsible for monitoring.

12. In the case of activated carbon adsorption beds, a warning that exhausted or contaminated carbon should be discarded and replaced with new beds.

13. For devices regenerated or reconstituted off-site, instructions on how to safely reconnect the device to the water treatment system and how to remove any contaminant or disinfectant in the device before use.

14. A statement on regenerated or reconstituted devices, such as deionizers, certifying that there was no intermixing of regenerated or reconstituted devices returned from medical or potable water users and devices returned from process or nonpotable water users. A statement that a description of the methods used to ensure that no intermixing occurred is available on request.

15. For automatically regenerated water treatment devices, identification of the mechanism (for example, lock-out valves) that prevents excessive levels of contaminants entering the product water during regeneration.

16. In the case of deionizers, a warning that deionizers should be preceded by an activated carbon adsorption bed and a recommendation that they be followed by an ultrafilter or other bacteria- and endotoxin-reducing device.

17. In the case of ultraviolet (UV) irradiators, a requirement that the manufacturer disclose the effectiveness of the device in killing specific bacteria under specified operating conditions, and a recommendation that UV irradiators be followed by an ultrafilter or other bacteria- and endotoxin-reducing device.

18. In the case of hot water disinfection systems, a requirement that the manufacturer disclose the effectiveness of the system in killing specific bacteria under specified operating conditions.

19. In the case of ozone disinfection systems, a requirement that the manufacturer disclose the effectiveness of the system in killing specific bacteria under specified operating conditions and provide a warning that product water shall not be used until the minimum time required for ozone to dissipate has elapsed.

20. In the case of hot water disinfection systems, a warning that appropriate heat-resistant materials be used for the fluid pathways to be disinfected with hot water.

21. In the case of ozone disinfection systems, a warning that appropriate ozone-resistant materials be used for the fluid pathways to be disinfected with ozone.

22. Construction materials, identified generically, that contact water.

23. Typical life expectancy, capacity, or indication of the end of life of components that are nondurable or require periodic regeneration or reconstitution, and a statement that additional information on component life expectancy or capacity relative to the user's typical feed water is available upon request. In the case of carbon adsorption beds, manufacturers or suppliers should provide a warning that unexpected exhaustion may occur because of variable feed water characteristics, including increasing pH, the presence of species that may compete for adsorption or reaction sites on the carbon media, or materials that are deposited on the surface of the carbon media, thereby preventing chlorine and chloramines from reaching adsorption or reaction sites on the carbon granules. The only safeguard against such unforeseeable eventualities is diligent monitoring of carbon filter effluent by the user.

24. Specified water supply or operating conditions that may cause the device to fail.

25. Information about germicides and cleaning agents known to be compatible with materials used in the device, as well as information about chemicals with which materials used in the device are incompatible.

26. If applicable, a method of cleaning and disinfecting the equipment, and of removing residual germicide, so that the system of which the equipment is part is capable of meeting the requirements for microbial and endotoxin contamination given in 4.2.1.

27. Other maintenance and service instructions, including recommended preventive maintenance procedures and schedules, recommended monitoring schedules, troubleshooting guidelines intended for the user, service information, a recommended spare parts list, and a warning of the consequences if maintenance instructions are not followed.

28. A warning that if, after installation and subsequent use, any component of the water treatment system is changed or replaced, the user should conduct appropriate tests to ensure that the revised system meets the initial design criteria.

4.2 Product water quality requirements

The requirements contained in this standard apply to the purified water as it enters the equipment used to prepare concentrates from powder at a dialysis facility, to prepare dialysate, or to reprocess dialyzers for multiple use. As such, these requirements apply to the water treatment system as a whole and not to each of the individual devices that make up the system. However, collectively the individual devices must produce water that, at a minimum, meets the requirements of the section.

4.2.1 Water bacteriology

Product water used to prepare dialysate or concentrates from powder at a dialysis facility, or to reprocess dialyzers for multiple use, should contain a total viable microbial count of less than 200 CFU/mL and an endotoxin concentration of less than 2 EU/mL. The action level for the total viable microbial count in the product water shall be 50 CFU/mL and the action level for the endotoxin concentration shall be 1 EU/mL. If these action levels are observed in the product water, corrective measures, such as disinfection and retesting, shall be taken promptly to reduce the levels into an acceptable range.

The manufacturer or supplier of a complete water treatment and distribution system shall demonstrate that the complete water treatment, storage, and distribution system is capable of meeting the requirements of this standard, including those related to action levels, at the time of installation.

Following installation of a water treatment, storage, and distribution system, the user is responsible for continued monitoring of the water bacteriology of the system and for complying with the requirements of this standard, including those requirements related to action levels.

4.2.2 Maximum level of chemical contaminants

Product water used to prepare dialysate or concentrates from powder at a dialysis facility, or to reprocess dialyzers for multiple use, shall not contain chemical contaminants at concentrations in excess of those in Table 1. The manufacturer or supplier of a complete water treatment system shall recommend a system capable of meeting the requirements of this clause given the analysis of the feed water. The system design should reflect possible seasonal variations in feed water quality. The manufacturer or supplier of a complete water treatment and distribution system shall demonstrate that the complete water treatment, storage, and distribution system is capable of meeting the requirements of this standard at the time of installation.

Following installation of a water treatment, storage, and distribution system, the user is responsible for continued monitoring of the levels of chemical contaminants in the water and for complying with the requirements of this standard.

Table 1—Maximum allowable chemical contaminant levels in water used to prepare dialysate and concentrates from powder at a dialysis facility and to reprocess dialyzers for multiple use[a)]

Contaminant	Maximum Concentration (mg/L)[b)]
Calcium	2 (0.1 mEq/L)
Magnesium	4 (0.3 mEq/L)
Potassium	8 (0.2 mEq/L)
Sodium	70 (3.0 mEq/L)
Antimony	0.006
Arsenic	0.005
Barium	0.10
Beryllium	0.0004
Cadmium	0.001
Chromium	0.014
Lead	0.005
Mercury	0.0002
Selenium	0.09
Silver	0.005
Aluminum	0.01
Chloramines	0.10
Free chlorine	0.50
Copper	0.10
Fluoride	0.20
Nitrate (as N)	2.00
Sulfate	100.00
Thallium	0.002
Zinc	0.10

[a)] The physician has the ultimate responsibility for ensuring the quality of water used for dialysis.

[b)] Unless otherwise noted.

4.3 Water treatment equipment requirements

4.3.1 General

The supplier of a water treatment system or a laboratory specified by the physician shall perform chemical analyses on feed water to determine the compatibility of the system with the feed water and the suitability of the system for providing product water meeting the requirements of 4.2.2. The result of the chemical analyses shall be available to the physician in charge of dialysis. In the case of an individual device, the person incorporating the device into the water treatment system is responsible for ensuring that incorporation of the device does not compromise the ability of the overall system to deliver product water capable of meeting the requirements of 4.2.2.

4.3.2 Materials compatibility

The materials of any components of water treatment systems (including piping, storage, and distribution systems) that contact the purified water shall not interact chemically or physically so as to adversely affect the purity or quality

of the product water. Such components shall be fabricated from unreactive materials (e.g., plastics) or appropriate stainless steel. The use of materials that are known to cause toxicity in hemodialysis, such as copper, brass, galvanized material, or aluminum, is specifically prohibited. Chemicals infused into the water, such as iodine, acid, flocculants, and complexing agents, shall be shown to be nondialyzable or shall be adequately removed from product water; monitors or specific test procedures to verify removal of additives shall be provided.

4.3.3 Disinfection protection

When the manufacturer recommends chemical disinfectants (see 4.1.2(26)), means shall be provided to restore the equipment and the system in which it is installed to a safe condition relative to residual disinfectant prior to the product water being used for dialysis applications. When recommending chemical disinfectants, the manufacturer shall also recommend methods for testing for residual levels of the disinfectants. When disinfection is accomplished automatically by chemical disinfectant, including ozone, or by high temperature procedures, activation of the disinfection system shall result in activation of a warning system and measures to prevent patient exposure to an unsafe condition.

4.3.4 Safety requirements

Each water treatment device shall exhibit the following minimum safety requirements (additional safety requirements specific to individual types of devices are listed in the appropriate subclauses of 4.3):

1. Monitors shall be designed so that the monitor cannot be disabled while a patient is at risk, except for brief, necessary periods of manual control with the operator in constant attention.

2. The sound emitted by audible alarms shall be at least 65 decibels (“A” scale) at 3 meters and it shall not be possible to silence these alarms for more than 180 seconds.

3. Resistivity, conductivity, or totally dissolved solids (TDS) monitors shall be temperature compensated.

4. Operating controls shall be positioned so as to minimize inadvertent resetting.

5. Electrical circuits shall be separate from hydraulic circuits and adequately protected from fluid leaks.

4.3.5 Regenerated or reconstituted devices

All devices that are regenerated or reconstituted off-site, such as deionizers, shall be disinfected at the time of regeneration or reconstitution so that contaminated water is not reintroduced into the system after regeneration or reconstitution. Separate processes shall be employed to ensure no intermixing of devices or their components between devices returned from medical or potable water users and devices returned from nonpotable water users.

4.3.6 Deionization

Deionization systems, when used to prepare water for hemodialysis applications, shall be monitored continuously to produce water of one megohm/cm or greater specific resistivity (or conductivity of one microsiemen/cm or less) at 25 °C. An audible and visual alarm shall be activated when the product water resistivity falls below this level and the product water stream shall be prevented from reaching any point of use, for example by being diverted to drain. (Deionizers used to prepare water for home hemodialysis or for portable dialysis systems are exempt from the requirement for diversion of flow.) The alarm must be audible in the patient care area. Feed water for deionization systems shall be pretreated with activated carbon adsorption, or a comparable alternative, to prevent nitrosamine formation. If a deionization system is the last process in a water treatment system, it shall be followed by an ultrafilter or other bacteria- and endotoxin-reducing device.

4.3.7 Reverse osmosis

The following requirements shall apply to reverse osmosis systems:

1. When used to prepare water for hemodialysis applications, either alone or as the last stage in a purification cascade, reverse osmosis systems shall be shown to be capable, at installation, of meeting the requirements of Table 1, when tested with the typical feed water of the user, in accordance with the methods of 5.2.2.

2. Reverse osmosis devices shall be equipped with on-line monitors that allow determination of rejection rates and product water conductivity. The product water conductivity monitor should activate audible and visual alarms when the product water conductivity exceeds the preset alarm limit. The audible alarm must be audible in the patient care area when reverse osmosis is the last chemical purification process in the water treatment system. Monitors that measure resistivity or TDS may be used in place of conductivity monitors.

In addition, it is recommended that when a reverse osmosis system is the last chemical purification process in the water treatment system, it includes a means to prevent patient exposure to unsafe product water, such as diversion of the product water to drain, in the event of a product water conductivity or rejection alarm.

4.3.8 Sediment filters

Sediment filters shall have an opaque housing or other means to inhibit proliferation of algae.

4.3.9 Carbon adsorption media

Carbon adsorption systems shall be adapted specifically to the maximum anticipated water flow rate of the system. Two carbon adsorption beds shall be installed in a series configuration. A means shall be provided to sample the product water from the first bed. Exhausted carbon adsorption media shall be discarded and replaced with new media according to a replacement schedule determined by regular monitoring. For example, when testing between the beds shows that the first bed is exhausted, the second bed should be moved into the first position, the second bed replaced with a new bed, and the exhausted bed discarded. When granulated activated carbon is used as the adsorption medium, the carbon shall have a minimum iodine number of 900 and each adsorption bed shall have an EBCT of at least 5 minutes at the maximum product water flow rate (a total EBCT of at least 10 minutes). When other forms of carbon are used, the manufacturer shall provide performance data to demonstrate that each adsorption bed has the capacity to reduce the chloramine concentration in the feed water to less than 0.1 mg/L when operating at the maximum anticipated flow rate for the maximum time interval between scheduled testing of the product water for chloramines. Regenerated carbon shall not be used. (Carbon adsorption systems used to prepare water for home dialysis or for portable dialysis systems are exempt from the requirement for the second carbon and a 10-minute EBCT, provided that removal of chloramines to below 0.1 mg/L is verified before each treatment.)

4.3.10 Automatically regenerated water softeners

Automatically regenerated water softeners shall be fitted with a mechanism to prevent water containing the high concentrations of sodium chloride used during regeneration from entering the product water line during regeneration. It is recommended that the face of the timers used to control the regeneration cycle be visible to the user.

4.3.11 Storage tanks

When used, storage tanks should have a conical or bowl-shaped base and should drain from the lowest point of the base. Storage tanks should have a tight-fitting lid and be vented through a hydrophobic 0.2-micron air filter. Means shall be provided to effectively disinfect any storage tank installed in a water distribution system.

4.3.12 Ultrafilters

When used in a water purification system for hemodialysis applications, an ultrafilter shall be shown to reduce the concentrations of bacteria and endotoxin in the feed water to the ultrafilter by factors at least as great as those specified in the manufacturer's labeling. It is recommended that ultrafilters be configured in a cross-flow mode. However, dead-end filters that have validated endotoxin and bacterial removal characteristics may also be used. It is recommended that ultrafilters have an opaque housing or that other means be used to inhibit proliferation of algae.

4.3.13 Ultraviolet irradiators

When used to control bacterial proliferation in water storage and distribution systems, UV irradiation devices shall be fitted with a low-pressure mercury lamp that emits light at a wavelength of 254 nm and provides a dose of radiant energy of 30 milliwatt-sec/cm^2. The device shall be sized for the maximum anticipated flow rate according to the manufacturer's instructions and shall be equipped with an on-line monitor of radiant energy output that activates a visual alarm indicating that the lamp must be replaced. It is recommended that UV irradiators be followed by an ultrafilter.

4.3.14 Hot water disinfection systems

When used to control bacterial proliferation in water treatment, storage, and distribution systems, the water heater of a hot water disinfection system shall be capable of delivering hot water at the temperature and for the exposure time specified by the manufacturer.

4.3.15 Ozone disinfection systems

When used to control bacterial proliferation in water storage and distribution systems, an ozone generator shall be capable of delivering ozone at the concentration and for the exposure time specified by the manufacturer. When ozone disinfection systems are used, it is recommended that an ambient air ozone monitor be installed in the area of the ozone generator.

4.3.16 Tempering valves

Tempering valves shall be sized to accommodate the anticipated range of flow rates of hot and cold water. They shall be fitted with check valves to prevent backflow of water into the hot and cold water lines and with a means to monitor the outlet water temperature.

4.3.17 Piping systems

The product water distribution system shall not contribute chemicals (such as aluminum, copper, lead, and zinc) or bacterial contamination to the treated water. Both direct and indirect water distribution systems should be configured as a continuous recirculation loop and designed to minimize bacterial proliferation and biofilm.

5 Tests

This clause defines test methods by which compliance with the requirements of clause 4 can be verified. The subclause numbers below correspond with the subclause numbers of clause 4.

NOTE—The test methods listed do not represent the only acceptable test methods available but are intended to provide examples of acceptable methods. Other test methods may be used where comparable sensitivity and specificity can be demonstrated.

5.1 Compliance with labeling and documentation requirements

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

5.2 Compliance with product water quality requirements

The requirements of 4.2.1 and 4.2.2 apply to the purified water as it enters the equipment used to prepare concentrates from powder at a dialysis facility, to prepare dialysate, or to reprocess dialyzers. As such, these requirements apply to the water treatment system as a whole and not to each of the individual devices that make up the system. However, collectively, the individual devices must produce water that meets the requirements of 4.2.1 and 4.2.2.

5.2.1 Water bacteriology

Samples shall be collected at a point where water enters the equipment used to prepare concentrates and dialysate, or the equipment used to reprocess dialyzers, or any other point where product water is dispensed. Samples shall be assayed within 30 minutes of collection or shall be immediately stored at 4–6 °C and assayed within 24 hours of collection. Total viable counts (standard plate counts) shall be obtained using the membrane filter technique, which can include commercial water-testing devices, or spread plates. The calibrated loop technique shall not be used. Culture media should be tryptic soy agar or equivalent. Blood agar and chocolate agar shall not be used. Incubation is at 35–37 °C and colonies shall be counted after 48 hours of incubation. Product water should not contain a total viable microbial count of $\geq$ 200 CFU/mL. Endotoxin concentrations shall be determined by the LAL assay and in no case should be $\geq$ 2 EU/mL.

5.2.2 Maximum level of chemical contaminants

Chemical analyses of the water contaminants listed in Table 1 of 4.2.2 shall be obtained by using methods referenced in the American Public Health Association's *Standard Methods for the Examination of Water and Wastewater* (see 2.3), methods referenced in the U.S. Environmental Protection Agency's *Methods for the Determination of Metals in Environmental Samples* (see 2.4), and/or other equivalent analytical methods. Samples shall be collected at the end of the water purification cascade and at the most distal point in each water distribution loop. All other outlets from the distribution loops shall be inspected to ensure that the outlets are fabricated from compatible materials (see 4.3.2). Appropriate containers and pH adjustments shall be used to ensure accurate determinations. Table 2 lists the test for each element, along with a reference to the appropriate normative reference.

Table 2—Analytical tests for chemical contaminants

Contaminant	Test Name	Applicable Document, Test Number
Aluminum	Atomic Absorption (electrothermal)	2.3, #3113
Antimony	Atomic Absorption (platform)	2.4, #200.9
Arsenic	Atomic Absorption (gaseous hydride)	2.3, #3114
Barium	Atomic Absorption (electrothermal)	2.3, #3113
Beryllium	Atomic Absorption (platform)	2.4, #200.9
Cadmium	Atomic Absorption (electrothermal)	2.3, #3113
Calcium	EDTA Titrimetric Method, or Atomic Absorption (direct aspiration), or Ion Specific Electrode	2.3, #3500-Ca D 2.3, #3111B
Chlorine and Chloramines	DPD Ferrous Titrimetric Method, or DPD Colorimetric Method	2.3, #4500-Cl F 2.3, #4500-Cl G
Chromium	Atomic Absorption (electrothermal)	2.3, #3113
Copper	Atomic Absorption (direct aspiration), or Neocuproine Method	2.3, #3111 2.3, #3500-Cu D
Fluoride	Ion Selective Electrode Method, or SPADNS Method	2.3, #4500-F^- C 2.3, #4500-F^- D
Lead	Atomic Absorption (electrothermal)	2.3, #3113
Magnesium	Atomic Absorption (direct aspiration)	2.3, #3111
Mercury	Flameless Cold Vapor Technique (Atomic Absorption)	2.3, #3112
Nitrate	Cadmium Reduction Method	2.3, #4500-NO_3 E
Potassium	Atomic Absorption (direct aspiration), or Flame Photometric Method, or Ion Specific Electrode	2.3, #3111 2.3, #3500-K D 2.3, #3500-K E
Selenium	Atomic Absorption (gaseous hydride), or Atomic Absorption (electrothermal)	2.3, #3114 2.3, #3113
Silver	Atomic Absorption (electrothermal)	2.3, #3113
Sodium	Atomic Absorption (direct aspiration), or Flame Photometric Method, or Ion Specific Electrode	2.3, #3111 2.3, #3500-Na D
Sulfate	Turbidimetric Method	2.3, #4500-SO_4^{2-} E
Thallium	Atomic Absorption (platform)	2.4, 200.9
Zinc	Atomic Absorption (direct aspiration), or Dithizone Method	2.3, #3111 2.3, #3500-Zn D

5.3 Compliance with water treatment equipment requirements

5.3.1 General

The need for tests to determine the quality of water used to feed water treatment equipment is dependent upon specific features of the devices. Suppliers of water treatment devices should select and perform such tests (e.g., iron, pH, silica, total dissolved solids, alkalinity, and total hardness) as are necessary to ensure the reliable performance of their devices.

5.3.2 Materials compatibility

The biocompatibility of materials used in components of the water treatment system in contact with the water can be verified using the tests described in the *United States Pharmacopeia* (see 2.5), such as USP class VI testing or leach testing with chemical analysis of the extractables.

5.3.3 Disinfection protection

Compliance with the requirements of 4.3.3 for chemical disinfection procedures can be determined by testing for the disinfectant in the product water at the end of the disinfection procedure. When the disinfectant is formaldehyde, residual levels can be determined by the Hantszch reaction, Schiff's reagent, or an equivalent test and shall be less than 5 mg/L. If a commercially available chemical germicide other than formaldehyde is used, an established test for residual germicide shall be used according to the test manufacturer's instructions, and the residual level shall be less than that recommended by the manufacturer of the specific germicide. Compliance with the requirements of 4.3.3 for high-temperature disinfection can be shown by demonstrating that the product water has returned to a safe temperature. Compliance with the requirements of 4.3.3 for ozone disinfection can be shown by demonstrating that the ozone concentration in the product water has returned to a safe level. Compliance with the patient protection requirements of 4.3.3 can be demonstrated by inspection.

5.3.4 Safety requirements

Compliance with 4.3.4(1), 4.3.4(3), 4.3.4(4), and 4.3.4(5) can be determined by inspection. Compliance with 4.3.4(2) shall be determined by use of an audiometer. Sound level measurements shall be made at a point 3 meters from the audible alarm. The standard "A" scale frequency response characteristics shall be used. Alarms capable of being silenced shall be made to alarm and then be silenced. A stopwatch shall be used to verify that the alarm sounds again after an interval of no more than 180 seconds.

5.3.5 Regenerated or reconstituted devices

The adequacy of disinfection procedures can be demonstrated by culturing a sample of the device's product water following the disinfection procedure. Where regenerated or reconstituted devices are provided by a vendor as medical devices, the disinfection and intermixing requirements of 4.3.5 may be demonstrated by certification that the device has been disinfected using validated procedures during regeneration or reconstitution and that validated procedures have been used to ensure that the devices and their components have been kept separate from devices and components used in nonpotable water applications.

5.3.6 Deionization

Resistivity measurements for product water of deionizers may be accomplished using conventional resistivity cells that incorporate temperature compensation features. The presence of required safety systems can be verified by inspection.

5.3.7 Reverse osmosis

1. Compliance with the requirement of 4.3.7(1) can be determined by the tests of 5.2.2.

2. Conductivity, resistivity, or TDS measurements of product water of reverse osmosis devices may be accomplished by using conventional monitors that incorporate temperature compensation features.

5.3.8 Sediment filters

Compliance with this requirement can be determined by visual inspection.

5.3.9 Carbon adsorption media

Chlorine removal can be used as an indication of carbon adsorption capacity. A DPD test kit selected for this purpose or a similar method shall be used to detect chloramine breakthrough, carbon exhaustion, or both. DPD materials shall be those designed for chlorine detection and shall be used according to manufacturers' instructions. Tests for total chlorine, which includes both free and combined forms of chlorine, may be used as a single analysis to safeguard both patients and chlorine-sensitive components. When total chlorine tests are used, the maximum allowable concentration is 0.1 mg/L, reflecting the maximum level allowed for patient exposure to chloramines (combined chlorine). Tests for both free and combined chlorine may also be performed to determine if chloramines are present. The difference between total chlorine and free chlorine shall be considered chloramines. The utility of such tests is dependent upon the sensitivity and detection limits of the analytical methods used. For example, an optical system having a detection limit of 0.1 mg/L will not yield valid data on chloramines if the concentration of free chlorine is less than the detection limit of the assay. In this example, patient safety considerations require that all of the chlorine measured as total chlorine be assumed to be in the form of chloramines, for which the maximum patient

exposure limit is 0.1 mg/L. Alternative tests (e.g., titrometry) should be used to follow up questionable results. Tests are not required for organic or radioactive materials.

5.3.10 Automatically regenerated water softeners

Compliance with the requirements of 4.3.10 can be determined by inspection.

5.3.11 Storage tanks

Compliance with the requirements of 4.3.11 can be determined by visual inspection.

5.3.12 Ultrafilters

Compliance with the requirements of 4.3.12 can be shown using the test methodologies for determining bacteria and endotoxin given in 5.2.1. Compliance with the requirement for protection against algae proliferation can be determined by visual inspection.

5.3.13 Ultraviolet irradiators

Compliance with the requirements of 4.3.13 can be determined by visual inspection.

5.3.14 Hot water disinfection systems

Compliance with the requirements of 4.3.14 can be determined by measuring water temperatures in the fluid pathway being disinfected for the disinfection time specified by the manufacturer.

5.3.15 Ozone disinfection systems

Compliance with the requirements of 4.3.15 can be determined by using an on-line monitor for dissolved ozone or by analysis of water samples using test kits based on indigo trisulfonate chemistry.

5.3.16 Tempering valves

Compliance with the requirements of 4.3.16 can be determined by visual inspection.

5.3.17 Piping systems

The absence of copper, lead, and zinc components and the configuration of a water treatment device or system can be determined by visual inspection. Noncontribution of bacteria and specific chemical contaminants to the water by the distribution system can be verified by using the tests described in 5.2.1 and 5.2.2.

Annex A
(informative)

Rationale for the development and provisions of this standard

A.1 Introduction

The development of a hemodialysis systems standard began in the late 1960s as a collaborative effort between the American Society for Artificial Internal Organs (ASAIO) and the Association for the Advancement of Medical Instrumentation (AAMI).

A standard was published in draft form and balloted by the committee several times during the 1970s, and a March 1979 draft was ultimately approved. Shortly thereafter, however, the committee became aware of work ongoing at the Minneapolis Medical Research Foundation, Regional Kidney Disease Program, under contract to the U.S. Food and Drug Administration's Bureau of Medical Devices, to identify the risks and hazards associated with conventional hemodialysis systems.

The AAMI Renal Disease and Detoxification Committee determined that it would be desirable to await the final publication of this report before finalizing the AAMI standard. The final FDA report was made available to the public in June 1980.

The AAMI Technology Assessment Conference "Issues in Hemodialysis," held in January 1981, provided an opportunity for more than 150 people in the hemodialysis field to convene to discuss and refine the standard. Subsequently, many of the recommendations of the FDA report and the AAMI conference were incorporated into the first edition of the American National Standard *Hemodialysis systems*, which was finally approved in May 1982.

The AAMI Renal Disease and Detoxification Committee initiated a thorough review of the *Hemodialysis systems* standard in 1986, recognizing that the technology of hemodialysis had changed in a number of respects since the standard was originally written. In particular, bicarbonate dialysis and "high-flux" dialysis had become common. Task groups were established in those areas that the committee felt needed most careful review, including bicarbonate dialysis, UFR controls, monitors, and microbiological aspects. As a result of the work of those task groups and review by the full committee, a proposed revision of the standard was prepared. The principal areas of change were the addition of provisions for bicarbonate dialysis, including color coding and labeling requirements to distinguish among the types of concentrate and proportioning ratios, and the addition of requirements for ultrafiltration controls or monitors. The basic microbiological requirements were not changed, but a section on bacteriology of aqueous bicarbonate concentrate was added. The committee concluded that, on the basis of available data, the introduction of highly permeable membranes did not require the establishment of limits on pyrogens in water for dialysis. The allowable levels of chemical contaminants in dialysis water were not changed.

Following committee ballot and public review, the second edition of the American National Standard *Hemodialysis systems* was approved on 16 March 1992.

The AAMI Renal Disease and Detoxification Committee initiated a further review of the *Hemodialysis systems* standard in 1996. At the beginning of this review, the committee made a decision to split the original *Hemodialysis systems* standard into three separate standards covering water, equipment, and concentrates. The performance of most water treatment devices changes with time in a manner dependent on the intensity of their use and the level to which they are maintained. For this reason, it became clear during the review process that a manufacturer of a device used to purify, store, and distribute water for hemodialysis applications could not necessarily be held responsible for the long-term performance of the device after it was installed and its proper operation verified. Accordingly, the committee decided to separate the water standard into two separate documents, a standard that covered devices used to purify, store, and distribute water and a recommended practice that was aimed at the users of these devices. The committee also decided to generalize the standard to cover all uses of water in hemodialysis, including for the preparation of dialysate and concentrates, and in the reprocessing of dialyzers for multiple use. Finally, the committee attempted to reconcile the standard with the FDA's guidelines for water purification devices used in hemodialysis applications that were issued in 1997 (*Guidance for the Content of Premarket Notifications for Water Purification Components and Systems for Hemodialysis* (see 2.1)), although not all of the FDA requirements were adopted. The principal area in which the content of the standard was changed was the requirements for the microbiological quality of the water. The committee felt that the preponderance of data published since the 1992 revision of the standard warranted inclusion of a limit for endotoxin in the product water. The concept of action levels was also included as a measure to help reduce the overall microbiological burden in the water.

This appendix contains the rationale for each of the specific provisions of the standard.

NOTE—AAMI Technology Assessment Report No. 2-81, *Issues in Hemodialysis: Systems Performance, Water Purity and Treatment, Cost Reimbursement, and Regulation*, provides additional technical rationale for the standard, as well as further historical background information and an update on the then-current cost reimbursement and regulatory policies for hemodialysis systems.

A.2 Scope of, and need for, the standard

The items included within the scope of this standard are equipment used to purify water for the preparation of concentrates and dialysate, or for the reprocessing of dialyzers for multiple use, and the devices used to store and distribute this water.

This standard seeks to prevent the use of options that are hazardous to patients treated with hemodialysis. For example, the standard is needed to prevent poisoning caused by formulation of dialysate with water containing high levels of certain contaminants.

Although the principal concern of the committee was for adequate, safe treatment of the patient, other considerations have influenced the standards for theoretical hazards, or remote, mild risks. Hemodialysis is a complicated and expensive procedure. The cost of treating end-stage renal disease (ESRD) patients, much of which goes toward hemodialysis, exceeded $15 billion in 1997, and prudence, efficiency, and reasonable cost-effectiveness are required for this standard to apply. Most hemodialysis procedures are performed in outpatient facilities, where many patients are treated simultaneously. Because many patients are at risk if a water treatment system fails in an outpatient facility, this standard focuses on protecting patients in this setting. However, dialysis also is performed in situations involving a single patient. Despite declining numbers of home hemodialysis patients, care in that setting is believed desirable. Also, single patients may be treated in an acute hospital setting where dialysis equipment is taken to the patient's bedside. Although a common standard for chemical and microbiological quality of water should apply in all settings, the committee recognizes that the need for portability may necessitate relaxation of some of the equipment design standards in the home or mobile acute dialysis settings. When less rigorous design standards are allowed, however, the onus is on the user to ensure appropriate water quality through increased monitoring and maintenance of the water treatment system.

The committee, therefore, has attempted to set standards that are consistent with cost constraints and user convenience whenever possible. Stringent standards have been reserved for serious threats to the patient or for specifications that are readily achievable at low cost with a minimum of inconvenience to the user. More liberal standards have been chosen when the risk to the patient is low and a large safety factor approaches the limits of available instruments, requires expensive modifications, or poses significant problems for the user.

A.3 Responsibility for compliance with the standard

Water treatment and distribution systems incorporate a variety of devices. These devices may be provided and installed by different vendors, making it difficult to assign responsibility for compliance with this standard to any one individual or company. To address this concern, the AAMI Renal Disease and Detoxification Committee chose to place primary responsibility for compliance with the standard on the individual or company that specifies the water treatment and distribution system installed in a given situation. The committee recognizes that responsibility may also lie with the vendor that assembles and installs the system, and with the manufacturer of any individual component of the water treatment and distribution system if that manufacturer specifies that its component is intended for hemodialysis applications.

A.4 Rationale for the specific provisions of this standard

This section contains the rationale for each of the requirements of clause 4 of this standard.

A.4.1 Labeling and documentation requirements

Existing federal regulations establish general requirements for the labeling of all medical devices, including such information as name and address of manufacturer and lot number. The committee felt, however, that redundancy of these requirements was preferable to omission, and it elected to require some of the same information already mandated by federal law. The provisions of the other requirements of 4.1 are intended to ensure that certain information specifically necessary for the safe and effective use of hemodialysis systems will be included in the device labeling. For most of this information, the underlying reasoning for the requirement is self-evident. Additional rationale for certain of these requirements is provided below.

Display of basic information about precautions before use is provided to ensure the safe and effective use of the device.

Purity of water used during dialysis is critical. Thus, the committee felt that certain information should be provided to the user so that appropriate precautions could be taken before the use of water for dialysis applications. The

specialized information of 4.1.2 reflects the committee's attempt to provide the user with sufficient information to minimize the risks of using improper water during dialysis.

A.4.2 Product water quality requirements

The AAMI Renal Disease and Detoxification Committee recognized that individual water treatment devices may not provide water that meets the requirements of this standard in its entirety. The previous revision of this standard (RD5:1992) required that the manufacturer or supplier of a water treatment device recommend a system capable of meeting the requirements of the standard. In preparing the 2000 revision, the committee felt that the number of potential contributors to a final water treatment and distribution system was too great to mandate this action of any one manufacturer. However, the committee believes that manufacturers of individual water treatment devices should be aware of the requirements for the final product water and that they should be prepared to recommend other water treatment devices that may need to be used in conjunction with their device to produce water which meets the requirements of this standard.

A.4.2.1 Water bacteriology

The supplier of water treatment equipment is responsible for recommending a method of cleaning the equipment so that product water meeting the microbial requirements of this standard can routinely be produced when typical feed water is presented. Beyond this qualification, it becomes the responsibility of the user of the system to monitor the system for ongoing compliance with the standard.

When this standard was initially developed, it was considered that neither the water used to prepare dialysate nor the dialysate itself needed to be sterile. However, several studies had demonstrated that the attack rates of pyrogenic reactions were related directly to the number of bacteria in dialysate (Dawids and Vejlsgaard 1976; Favero *et al.* 1974; Favero *et al.* 1975). These studies provided the rationale for setting the guidelines in the first edition of the hemodialysis standard at 2000 bacteria per mL in dialysate and at 200 bacteria per mL for the water used to prepare dialysate. In the latter case, it was known that if the level of contamination exceeded 200 bacteria per mL in water, this level could be amplified in the system and effectively constitute a high inoculum for dialysate at the start of a dialysis treatment. Even at low levels of bacterial contamination, pyrogenic reactions have been reported when the source of endotoxin was exogenous to the dialysis system (i.e. present in the community water supply) (Hindman *et al.* 1975). In addition, it had been shown that problems relating to microbial contamination in dialysis systems did not usually have a single cause, but rather were the result of a number of causes and factors involving the water treatment system, the water and dialysate distribution systems, and, in some cases, the type of hemodialyzer. Understanding the various factors and their influence on contamination levels is the key to preventing high levels of microbial contamination.

Several groups of investigators have shown convincingly that pyrogenic reactions are caused by lipopolysaccharides or endotoxins that are associated with gram-negative bacteria. Furthermore, gram-negative water bacteria have been shown to have the capability of multiplying rapidly in a variety of hospital-associated fluids, including distilled, deionized, reverse osmosis, and softened water, all of which can be used as supply water for hemodialysis systems. The dialysate, which is a balanced salt solution made with this water, likewise provides a very good growth medium for these types of bacteria.

Several investigators (Jones *et al.* 1970; Kidd 1964) have shown that bacteria growing in dialysate produced products that could cross the dialysis membrane. It has also been shown (Gazenfeldt-Gazit and Eliahou 1969; Raij *et al.* 1973) that gram-negative bacteria growing in dialysate produced endotoxins that in turn stimulated the production of anti-endotoxin antibodies in hemodialysis patients. These data suggest that bacterial endotoxins, although relatively large molecules, do indeed cross dialysis membranes, either intact or as fragments. The use of the very permeable membranes known as high-flux membranes has raised the possibility of a greater likelihood of passage of endotoxins into the blood path. Several studies support this contention. Vanholder *et al.* (1992) observed an increase in plasma endotoxin concentrations during dialysis against dialysate containing 10^3 to 10^4 CFU/mL *Pseudomonas* species. *In vitro* studies using both radiolabeled lipopolysaccharide and biological assays have demonstrated that biologically active substances derived from bacteria found in dialysate can cross a variety of dialysis membranes (Laude-Sharp *et al.* 1990; Evans and Holmes 1991; Lonnemann *et al.* 1992; Ureña *et al.* 1992; Bommer *et al.* 1996). Also, patients treated with high-flux membranes are reported to have higher levels of anti-endotoxin antibodies than normal subjects or patients treated with conventional low-flux membranes (Yamagami *et al.* 1990). Finally, the Centers for Disease Control and Prevention have reported that the use of high-flux dialyzers is a significant risk factor for pyrogenic reactions (Tokars *et al.* 1996). Although other investigators have not been able to demonstrate endotoxin transfer across dialysis membranes (Bernick *et al.* 1979; Bommer *et al.* 1987), the preponderance of reports now supports the ability of endotoxin to transfer across at least some high-flux membranes under some operating conditions. In addition to the acute risk of pyrogenic reactions, there is increasing indirect evidence that chronic exposure to low amounts of endotoxin may play a role in some of the long-term complications of hemodialysis therapy. Patients treated with ultrafiltered dialysate for 5 to 6 months have demonstrated a decrease in serum β_2-microglobulin concentrations (Quellhorst 1998) and a decrease in markers of an inflammatory response (Schindler *et al.* 1994; Akrum *et al.* 1997). In longer-term studies, use of microbiologically ultrapure dialysate has

been associated with a decreased incidence of β_2-microglobulin-associated amyloidosis (Baz *et al.* 1991; Schwalbe *et al.* 1997; Kleophas *et al.* 1998). Consequently, it seems prudent to impose an upper limit on the endotoxin content of the water. A level of 2 EU/mL was chosen as the upper limit for endotoxin, since these levels are easily achieved with contemporary water treatment systems using reverse osmosis, ultrafiltration, or both. Because 48 hours can elapse between sampling water for the determination of microbial contamination and receiving results, and because bacterial proliferation can be rapid, action levels for microbial counts and endotoxin concentrations were introduced in this revision of the standard. These action levels allow the user to initiate corrective action before levels exceed the maximum levels established by the standard.

In hemodialysis, the net movement of water is from the blood to the dialysate, although within the dialyzer there may be local movement of water from the dialysate to the blood through the phenomenon of back-filtration, particularly in dialyzers with highly permeable membranes (Leypoldt *et al.* 1991). In contrast, hemofiltration and hemodiafiltration feature infusion of large volumes of electrolyte solution (20 to 70 L) into the blood. Increasingly, this electrolyte solution is being prepared on-line from water and concentrate. The large volumes of fluid infused in hemofiltration and hemodiafiltration, and general concerns about the transfer of endotoxin and endotoxin fragments across high-flux membranes, have given rise to the concept of “ultrapure” fluids for use in dialysis applications. An “ultrapure fluid” is defined as one having a bacterial content of less than 0.1 CFU/mL and an endotoxin content of less than 0.03 EU/mL using sensitive assays (Ledebo and Nystrand 1999). This definition is now widely accepted, particularly in Europe, as the standard for use in on-line convective therapies. During the 2000 revision of this document, the committee considered adopting this standard for water to be used in hemofiltration and hemodiafiltration. However, because of insufficient experience with on-line therapies, the committee could not reach a consensus on the need for the more stringent requirements. On-line hemofiltration and hemodiafiltration systems use sequential ultrafiltration as the final step in the preparation of infusion fluid. Several committee members felt that these point-of-use ultrafiltration systems should be capable of reducing the bacteria and endotoxin burden of solutions prepared from water meeting the requirements of this standard to a safe level for infusion.

A.4.2.2 Maximum level of chemical contaminants

Contaminants identified as needing restriction on the allowable level that may be present in water for dialysis are divided into three groups for the purposes of this standard. The first group includes chemicals shown to cause toxicity in dialysis patients. These chemicals include fluoride, aluminum, chloramines, sulfate, nitrate, copper, and zinc. Chlorine is included here because of its potential toxicity.

Toxicity of fluoride in dialysis patients at the levels usually associated with fluoridated water, 1 part per million (ppm), is questionable. In the absence of a consensus on fluoride’s role in uremic bone disease, the committee initially thought it prudent to restrict the fluoride level of dialysate (Rao and Friedman 1975). Subsequently, illness in 8 of 8 dialysis patients, with the death of 1 patient, was reported as a result of accidental overfluoridation of a municipal water supply (CDC 1980). Fluoride levels of up to 50 ppm were found in water used for dialysis that was treated only with a water softener. Probably these illnesses would have been less severe, if not prevented, if the dialysis water had been treated with deionization or reverse osmosis. If deionization is used, implementation of the monitoring requirements listed in 4.3.4 must be closely adhered to. In one case, where deionizers were allowed to exhaust, 12 of 15 patients became acutely ill from fluoride intoxication (Arnow *et al.* 1994). Three of the patients died from ventricular fibrillation. Fluoride concentrations in the water used to prepare the dialysate were as high as 22.5 ppm.

The suggested maximum aluminum level has been specified to prevent accumulation of this toxic metal in the patient (Kovalchik *et al.* 1978). Aluminum is particularly likely to increase suddenly to high levels caused by changes in the method of water treatment to include aluminum-containing compounds. As with fluoride, water treatment would provide a measure of safety should the aluminum levels increase dramatically between chemical tests of the product water.

The toxicity of chloramines is undisputed (Eaton *et al.* 1973). Although the role of free chlorine in oxidative blood damage is unclear, its high oxidation potential and ability to form chloramines suggests the avoidance of highly chlorinated water in preparation of dialysate.

Sulfate at levels above 200 mg/L has been related to nausea, vomiting, and metabolic acidosis. The symptoms disappear when the level remains below 100 mg/L (Comty *et al.* 1974). Nitrates are a marker for bacterial contamination and fertilizer runoff, and have caused methemoglobinemia (Carlson and Shapiro 1970). They should, therefore, be permitted only at very low levels. Both copper and zinc toxicity have been demonstrated when these substances are present in dialysate at levels below those permitted by the U.S. Environmental Protection Agency (EPA) standard (Ivanovich *et al.* 1969; Petrie and Row 1977). Hence, a lower level has been chosen.

The second group of chemical contaminants is based on the EPA’s *Safe Drinking Water Act* (see 2.6). When this standard was initially developed, the *Safe Drinking Water Act* included barium, selenium, chromium, lead, silver, cadmium, mercury, and arsenic. Selenium and chromium levels were set at the “no-transfer” level (Klein *et al.* 1979). The “no-transfer” level was chosen even though it is above the EPA limit for selenium and 28 % of the EPA limit for chromium, because a restriction is not needed below the level at which there is no passage from the dialysate to the

blood. The standard specified the maximum allowable limits for the other contaminants in this group at one tenth of the EPA maximum allowable limits because the volume of water used for dialysis far exceeds that used for drinking water, because protein binding of these solutes may occur in the blood, and because there is reduced renal excretion of these substances. These reduced limits were selected using the following assumptions: (1) feed water entering dialysis systems typically meets the EPA *Safe Drinking Water Act* (see 2.6); (2) typically, reverse osmosis treatment removes 90 % to 99 % of dissolved inorganic solids; and (3) reverse osmosis-treated water is a suitable standard for safety of water used in dialysis. These assumptions are based on the recommendations of Keshaviah *et al.* (1980). The committee recognized that these assumptions are questionable but reasoned that setting standards in this way will cause little or no economic impact, even though some feed water exceeds the EPA maximum allowable levels. It should be noted that the level for arsenic, 0.05 mg/L, in the Keshaviah report is a typographical error. The correct value is 0.005 mg/L as given in Table 1 of this standard (E. Klein, personal communication).

At the time of the 2000 revision of this standard, several changes had occurred in the *Safe Drinking Water Act.* Specifically, antimony, beryllium, free cyanide and thallium had been added to the list of contaminants covered by the Act and the maximum allowable levels for cadmium and lead had been decreased. For consistency, the committee chose to add antimony, beryllium, and thallium to the standard. The maximum allowable levels of antimony and thallium were set at values above one-tenth of the EPA maximum allowable level because of limitations in the sensitivity of commonly available analytical methods for these two contaminants. After considerable discussion, the committee chose not to add free cyanide to the standard. There was concern that special requirements for sample collection and shipment, together with the need to pre-treat the sample before analysis to eliminate interfering substances, would impose a burden on dialysis facilities that could not be justified in the absence of specific toxicity data. More generally, the committee recognized that little, if any, data existed to indicate hemodialysis patients are at particular risk from the four contaminants noted above solely by virtue of their inclusion in the *Safe Drinking Water Act.* Therefore, the committee agreed that a comprehensive review of the toxicity of these contaminants in hemodialysis patients should be undertaken before the next scheduled review of ANSI/AAMI RD62:2001, *Water treatment equipment for hemodialysis applications*. The committee also decided not to decrease the maximum allowable levels of cadmium and lead in the standard. This decision was based on the absence of toxicity data in dialysis patients treated with water that meets the current standard and the minimum detection levels of currently used analytical methods.

The third group of substances addressed in 4.2.2 and Table 1 consists of physiological substances that can adversely affect the patient if present in the dialysate in excessive amounts. Calcium, potassium, and sodium are examples of these substances.

Of the physiological substances that can be harmful when present in excessive amounts, calcium has been reduced from the 10 ppm originally selected to 2 ppm, on the basis of the critical role of calcium in bone disorders associated with renal disease. A level of 10 ppm would have allowed a potential 20 % error in dialysate calcium, whereas a level of 2 ppm reduces that error risk to less than 5 %.

Table 1 of this standard should not be taken as a definitive list of harmful substances, but as a partial listing of those that might reasonably be expected to be present and have clinical implications. Iron is not included because it does not enter the patient's blood in sufficient quantities to cause toxicity. Iron may, however, cause fouling of water purification devices (see 4.3.1) or dialysate supply systems. While the AAMI Renal Disease and Detoxification Committee chose not to set a specific limit, water treatment equipment suppliers are encouraged to consider the iron content of the feed water when recommending suitable equipment. During the first revision of this standard, a concern was raised regarding the injection of formulated phosphates (known as polyphosphates) primarily to bind iron and manganese to avoid the staining of fixtures and clothing. The concern was raised that this practice could cause significant problems in water purification. At the time of the 2000 revision of the standard, some municipal water suppliers were considering the use of chlorine dioxide as a disinfectant for potable water supplies. Chlorine dioxide breaks down in water to yield chlorite, chlorate, and chloride ions. The committee could find little information about the potential for chlorine dioxide and its daughter products to be toxic to hemodialysis patients. A limited study of 17 patients unknowingly treated with purified water prepared by carbon adsorption and reverse osmosis from water disinfected with chlorine dioxide showed no evidence of adverse effects (Ames and Stratton 1987). In that study, the purified water used to prepare dialysate contained 0.02 to 0.08 mg/L of chlorite ions and no detectable chlorate ions. However, the patient population was small, and potentially important hematological parameters were not measured. Further, there was only sparse data included on the removal of chlorine dioxide, chlorite ions, and chlorate ions by carbon adsorption and reverse osmosis, and it was not clear that sufficiently sensitive methods were available for their analysis in a dialysis facility. Therefore, the committee concluded that there was no basis for setting maximum allowable levels of chlorine dioxide, chlorite ions, or chlorate ions in water to be used for dialysis applications, or for making recommendations on methods for their removal at that time. However, in specifying water purification systems, manufacturers of such systems should be aware of the possibility that municipal water suppliers may add chlorine dioxide to the water.

When the standard was originally developed, limits could not be set for toxic organic substances or for radioactive materials (Keshaviah *et al.* 1980). However, the committee noted that the EPA drinking water standard (see 2.6) lists maximum contaminant levels (MCL) for more than 50 toxic organic substances. Following the rationale used in

establishing levels for other potentially toxic contaminants that have not been shown to be harmful to dialysis patients (see previous paragraph), it is reasonable that these levels should be reduced tenfold if they are monitored. This data is provided for information purposes only, because these substances are only representative of a vast number of contaminants that occur in tap water, all of whose toxic effects are largely unknown (Keshaviah *et al.* 1980). The committee also agreed with the Keshaviah report that systems including reverse osmosis and carbon filtration would adequately remove most organics.

A.4.3 Water treatment equipment requirements

A.4.3.1 General

The supplier of the complete water treatment system is responsible for assuring that the water produced by the system can routinely meet the maximum allowable chemical contaminant levels specified in Table 1, or the prescription of the physician, at installation. Beyond this qualification, it becomes the responsibility of the physician in charge of dialysis to monitor the system to assure that the treatment device or devices maintain an acceptable level of purity of the water. Variations in water quality or the presence of as-yet-unidentified toxic substances will obviously compromise the system's safety (Keshaviah *et al.* 1980). Such variations typically do occur, and while the supplier cannot be held accountable for the performance of the water treatment system during such variations, selection of water purification equipment should include careful consideration of methods to cope with such changes, many of which may be anticipated through consultation with state and local water authorities.

The medical director has the ultimate responsibility for the selection and use of water purification devices on the basis of the supplier's recommendations. If a supplier is convinced that the local water quality is such that the selection of a minimum system does not provide an adequate margin of safety, then the supplier should recommend additions to the system or alternative systems with corresponding rationale. Continued monitoring of the water supply is necessary to maintain treatment methods consistent with safety.

A.4.3.2 Materials compatibility

Nontoxicity of construction materials for hemodialysis equipment is of major importance. Data is now available that demonstrates that materials once regarded as inert may in fact be toxic in this application (e.g., copper leaches from copper conduits, especially in the presence of low pH, which may result when a deionizer is exhausted) (Keshaviah *et al.* 1980). Other materials have been documented as being hazardous to the patient (e.g., brass, zinc, iron, and aluminum), and these materials should also be avoided. Some well-recognized nontoxic materials include certain stainless steel formulations, silicon rubber, borosilicate glass, polypropylene, polyvinylchloride (PVC), and polytetrafluorethylene (PTFE). The hidden hazard with respect to construction materials derives from long-term cumulative toxicity. Patients on hemodialysis may well have a life expectancy in excess of 10 years, and this fact must be acknowledged when selecting construction materials. Direct testing for chemicals leached from components cannot be specified at this time because of a lack of suitable procedures.

Repeated exposure to ozone or hot water may have a deleterious effect on some plastic or metal materials. Therefore, the committee chose to require manufacturers to include warnings that only ozone- or heat-compatible materials be used in piping systems intended for use with ozone or hot water disinfection devices, respectively (see 4.1.2).

A.4.3.3 Disinfection protection

Disinfection procedures may render product water unsafe because of toxic chemicals or excessive temperatures. Therefore, the committee felt that provision should be made for restoring the water treatment system to a safe condition after disinfection. Although the committee recognized that the user is responsible for carrying out manual disinfection procedures, the committee believes that the manufacturer should demonstrate that recommended disinfection procedures meet the requirements of 4.3.3.

A.4.3.4 Safety requirements

Although some of these requirements may seem obvious, the committee felt that all safety requirements should be specified. The question of whether or not audible alarms should be capable of being silenced provoked some discussion. On one hand, some felt that audible alarms should not be capable of being silenced because the alarm condition could be overlooked, allowing a dangerous situation to ensue. On the other hand, an audible alarm capable of being temporarily silenced was suggested so that the operator would have a relatively unharried period of time to correct the fault condition. The committee concluded that silencing an audible alarm for up to 180 seconds was a reasonable requirement.

A.4.3.5 Regenerated or reconstituted devices

Regenerated or reconstituted devices are subject to bacterial contamination that can cause excessive bacterial counts in product water (see 4.2.1). Disinfection procedures are required to minimize this risk. When devices are

regenerated at a central facility, there is a risk of cross-contamination and improper disinfection and rinsing (Keshaviah *et al.* 1980). Some exchange-type deionizers are used for both dialysis and industrial recovery of plating metals, such as chromium and silver, from effluent process water. In some regeneration facilities, resins from both process or nonpotable users and from medical or potable users are regenerated together as a batch. Traces of these toxic metals will remain bound to the resins and may be eluted into water during subsequent use. For that reason, the committee felt that such mixed use shall be prohibited.

A.4.3.6 Deionization

Deionizer systems, during exhaustion, have the capability of releasing into the water potentially harmful contaminants at levels much higher than are present in the untreated feed water (Johnson and Taves 1974; Bland *et al.* 1996). The monitor level of 1 megohm/cm specific resistivity was selected as the point at which most of the useful capacity of the deionizers used in dialysis water treatment has been consumed and below which rapid degradation of ion removal efficiency takes place. One megohm/cm specific resistivity is not the minimum safe value for dialysis water, but deionizer systems producing water dropping below this value are in danger, during the following dialysis treatment, of producing water high in toxic contaminants as final deterioration of resin accelerates. A requirement that the product water be diverted to drain was included because of the acute danger that an exhausted deionizer can pose to patients (Arnow *et al.* 1994). The requirement for activated carbon adsorption in advance of the deionizer prevents generation of possibly carcinogenic nitrosamines (Simenhoff *et al.* 1983). Deionizers are subject to bacterial contamination because of the porous structure of the resins. Although the level of bacterial contamination in product water from deionizers varies widely, it is generally highest after the deionizer has been idle for some time and lowest after continuous use. Because deionizers are usually placed last in a purification cascade, they should be followed by an ultrafilter to prevent bacterial contamination of the water storage and distribution system.

A.4.3.7 Reverse osmosis

A reverse osmosis system should demonstrate delivery of water meeting the requirements of 4.2.2; otherwise, additional treatment devices should be recommended to the user. Monitoring requirements for reverse osmosis systems are recommended on the basis of totally different degradation characteristics of these systems as compared with deionizer systems. On initial setup, the reverse osmosis device should have a rejection rate that ensures that the product water of the water treatment system meets the requirements of 4.2.2. Because this rejection rate varies with different installations, an absolute level is not required. Monitoring is defined in terms of the salt passage rate, or percent rejection, and a threshold level of product water resistivity or conductivity. Compliance with both monitored parameters is required, since an increase in feed water contaminants may result in product water unsuitable for hemodialysis applications even though the percent rejection of the membrane modules remains high.

The committee could not reach consensus on how to establish the alarm limits for rejection and product water resistivity or conductivity. As noted above, changes in feed water quality will result in changes in product water quality even though rejection remains constant. Also, a significant change in the feed water concentration of one trace inorganic contaminant may not appreciably alter the product water resistivity even though the product water concentration of that contaminant exceeds the allowable limit. For that reason, some committee members felt that routine analysis of feed water quality should be emphasized. Other committee members felt that the rejection alarm limit could be set based on the reduction ratio for each contaminant that can be achieved by reverse osmosis (Luehmann *et al.* 1989) and the assumption that the feed water would meet the requirements of the *Safe Drinking Water Act* (see 2.6). Either approach may be effective when incorporated into an overall monitoring program designed to protect the patient against exposure to contaminant levels in excess of those listed in Table 1.

The committee could not reach consensus regarding the inclusion of a requirement that reverse osmosis systems incorporate a means of diverting the product water to drain in the event of a product water conductivity or rejection rate alarm. Some committee members felt that a divert-to-drain should be required because reverse osmosis is frequently the primary means of water purification. However, other committee members felt that including a divert-to-drain should be optional. They pointed out that, because reverse osmosis membranes tend to fail gradually, the risk is different from exhaustion of a deionizer where very high levels of contaminants, such as fluoride, may occur abruptly in the product water because of competitive binding at the ion exchange sites of the deionizer resin. Furthermore, with direct feed water distribution systems, a divert-to-drain would cause an immediate alarm condition with all dialysis machines as a result of interrupting their water supply. Under such circumstances, the ability to discontinue dialysis electively may pose the least risk to the patients. Therefore, a divert-to-drain was included as a recommendation and not as a requirement.

A.4.3.8 Sediment filters

Accumulation of organics, bacteria, algae, etc., on filters can lead to proliferation of bacteria to the point of overloading downstream elements or producing dangerous endotoxin levels. Use of opaque housings to reduce the light that promotes algae growth and differential pressure monitoring can reduce this risk.

A.4.3.9 Carbon adsorption media

Carbon adsorption beds are particularly prone to bacterial infection because of their porosity and affinity for organics. More stringent requirements for the installation of carbon adsorption beds and their monitoring were included in the second revision of this standard because of continued reports of clusters of hemolysis related to insufficient removal of chloramines from municipal water supplies (Caterson *et al.* 1982; Tipple *et al.* 1991; Ward 1996). Changes to the *Safe Drinking Water Act*, designed to eliminate lead and copper from tap water (Petersen and Thomas 1991), reinforce the need for careful monitoring of carbon adsorption beds, since the increase in water pH that may accompany institution of these changes may decrease the adsorptive capacity of carbon for chloramines.

Activated carbon may be regenerated by a number of techniques, including oxidation at high temperatures and stripping with low-pressure steam or solvents. Regeneration of activated carbon, also known as reactivation, is used in industrial applications where activated carbon may be used to remove organic and inorganic substances such as pollutants from process streams. The committee could find no evidence that regenerated carbon was being used for hemodialysis applications. However, the committee felt that it was prudent to prohibit the use of regenerated carbon in hemodialysis applications to avoid any potential hazard resulting from residual toxins that may remain in the carbon following regeneration.

Depending on the source material used for its manufacture, and the manufacturing process, granular activated carbon may contain carbon fines and other contaminants, such as aluminum. If present, these substances will leach out of a carbon adsorption bed during the initial stages of operation. Carbon fines may contribute to fouling of reverse osmosis membranes downstream of the carbon adsorption beds and any metal ions may add to the burden of contaminants which must be removed from the water. Acid washing of carbon minimizes the amount of fines and other contaminants, and some committee members felt that use of acid-washed carbon should be required. No consensus could be reached on this issue, because rinsing of carbon adsorption beds before they are placed on-line in a water purification cascade will also effectively remove fines and other contaminants.

The requirement for two adsorption beds in series and a 10-minute empty bed contact time was waived for portable dialysis systems because of the impracticality of providing these features while retaining the portability of the system. However, when a single adsorption bed is used, it is important to ensure that the bed has adequate capacity to remove chloramines for the duration of an entire treatment given the typical feed water concentration of chloramines in the setting where the bed is being used.

Although treatment of water by carbon adsorption is the usual method of meeting the requirement of 4.2.2 for chloramines, the committee recognized that in certain situations, such as acute or home dialysis with portable water treatment systems, it may not be practical to use the volume of carbon required for this purpose. In such circumstances, combining limited carbon adsorption with the addition of ascorbic acid to the acid concentrate has been used to eliminate chloramines from the final dialysate (Ward 1996). It should be noted that some minimum contact time is required for ascorbic acid to neutralize chloramines in water. If ascorbic acid is being used to neutralize chloramines, and unexplained red cell destruction or anemia occurs, the effectiveness of the ascorbic acid neutralization of chloramines should be investigated.

A.4.3.10 Automatically regenerated water softeners

The process by which “hard” water (containing high levels of calcium and magnesium) is made “soft” involves the exchange of sodium ions for the calcium and magnesium in the water supply. The resin must be regenerated with brine to sustain capacity for exchange. Regeneration may be either manual or automatic with a timer to regenerate outside operating hours. During regeneration, excess sodium may enter the product water stream if there is a temporary interruption of power, a malfunction in regeneration control, or inadequate water pressure. There are no monitors on a softener to detect excess sodium in the product water stream, and the physiological effects of excess sodium in the patient are severe (Nickey *et al.* 1970; Robson 1978). Therefore, the committee felt strongly that a protection against such excessive levels of sodium, as may occur during regeneration of a water softener, should be required. An automatic bypass valve most easily provides this protection during the regeneration cycle.

A.4.3.11 Storage tanks

The large volume and low water velocities in storage tanks predispose them to bacterial contamination. As a consequence, these tanks must be designed with features to prevent entry of bacteria and to facilitate disinfection procedures.

A.4.3.12 Ultrafilters

Ultrafilters are increasingly being used to provide water of high microbiologic purity for dialysis applications. In general, ultrafilters are characterized by their molecular weight cut-off. However, in hemodialysis applications, the principal role of ultrafilters is to remove bacteria and endotoxins. Therefore, the committee chose to define ultrafilters in these terms. This choice also provides a basis for monitoring the performance of ultrafilters after they have been installed in a water purification system. The committee could not reach consensus regarding minimum performance

criteria for the removal of bacteria and endotoxins by an ultrafilter. Therefore, the committee chose to require that manufacturers disclose the minimum performance of their device and that the device be required to perform to at least this level. Individual members of the committee considered that an ultrafilter should be able to reduce the concentration of bacteria in the feed water to the ultrafilter by a factor of at least 10^7 and that of endotoxin by a factor of at least 10^3. The recommendation to use an ultrafilter in a cross-flow configuration is aimed at preventing excessive replacement of membrane modules, which may result from rapid fouling if the filter is operated in the dead-end mode. However, a dead-end configuration may perform satisfactorily in situations where the water quality is generally good (for example, as final filtration of purified water immediately before its use in dialyzer reprocessing equipment). Differential pressure measurements can be used to monitor fouling of both cross-flow and dead-end filters.

A.4.3.13 Ultraviolet irradiators

The effectiveness of UV irradiation depends on the dose of radiant energy. Several studies have demonstrated that a dose of 30 milliwatt-sec/cm^2 will kill greater than 99.99 % of a variety of bacteria, including *Pseudomonas* species, in a flow-through device (Martiny *et al.* 1988; Martiny *et al.* 1990). However, certain gram-negative water bacteria appear to be more resistant to UV irradiation than others, and use of sub-lethal doses of UV radiation, or an insufficient contact time, may lead to proliferation of these resistant bacteria in the water system (Carson and Petersen 1975). The radiant energy emitted by the mercury vapor lamps used in UV irradiators decreases with time. If the lamp is not replaced before its radiant energy decreases below the effective threshold, resistant bacteria may also develop. Therefore, the requirement for an on-line monitor of the radiant energy emitted by the lamp was included in the standard. Because the effectiveness of UV irradiation depends on the geometry of the device and the exposure time of water to the radiation, the manufacturer of a UV irradiation device is required to provide information on the killing of specific bacteria under specified operating conditions. Because UV irradiators do not eliminate endotoxin and may even increase endotoxin concentrations by killing bacteria, the committee recommended that they be followed by an ultrafilter. Use of an ultrafilter was not made a requirement, however, because reliance on an ultrafilter to remove endotoxin should not be considered an alternative to identifying and eliminating the source of bacterial contamination.

A.4.3.14 Hot water disinfection systems

At the time of the 2000 revision of this standard, hot water disinfection of purified water storage and distribution systems was being introduced as a new means of controlling bacterial proliferation. The committee recognized that this new technology might have widespread applicability in dialysis facilities in light of the increased concern about endotoxin contamination of dialysate (see A.4.2.1). However, at the time of the 2000 revision of the standard, insufficient data was available to set performance standards for such systems, such as water temperature and exposure time. Therefore, the committee chose to require that the manufacturer of a hot water disinfection system disclose the operating specifications of the system until such time as performance criteria could be established. The manufacturer of a hot water disinfection system should validate the recommended operating conditions to demonstrate that they provide adequate reduction in bacterial levels. Repeated exposure to hot water may have a deleterious effect on some plastic piping. Therefore, a requirement that manufacturers of hot water disinfection systems include a warning in their product labeling about the need to use heat-resistant materials in piping systems to be disinfected with hot water was added to the standard.

A.4.3.15 Ozone disinfection systems

At the time of the 2000 revision of this standard, ozonation was being introduced as a new means of controlling bacterial proliferation in purified water storage and distribution systems. The committee recognized that this new technology might have widespread applicability in dialysis facilities in light of the increased concern about endotoxin contamination of dialysate (see A.4.2.1). However, at the time of the 2000 revision of the standard, insufficient data was available to set performance standards for such systems, such as ozone concentration and exposure time. Therefore, the committee chose to require that the manufacturer of an ozone disinfection system disclose the operating specifications of the system until such time as performance criteria could be established. The manufacturer of an ozone disinfection system should validate the recommended operating conditions to demonstrate that they provide adequate reduction in bacterial and, if applicable, endotoxin levels. The presence of ozone in product water may be harmful to patients. Therefore, the committee chose to require manufacturers to include a warning that product water should not be used until ozone produced in the disinfection process has dissipated (see 4.1.2(19)). The manufacturer should validate that residual ozone in the product water falls to acceptable levels at the end of the recommended minimum elapsed time between disinfection and use of the product water. Alternatively, the manufacturer of an ozone disinfection system may provide the user with a means of verifying that the residual ozone is within acceptable limits before product water is used.

A.4.3.17 Piping systems

The distribution system has been implicated in several bacterial contamination episodes involving dialysis patients (Petersen *et al.* 1978). The AAMI Renal Disease and Detoxification Committee discussed including specific design

criteria, such as minimum flow velocities, to minimize bacterial proliferation and biofilm formation (Chapman *et al.* 1983). Differences in system configuration (for example, direct feed versus indirect feed) made it difficult to reach consensus on specific design criteria. However, the committee recommends a minimum velocity of 3 ft/s in indirect feed distribution systems. This velocity is sufficient to ensure non-laminar flow, which helps protect against biofilm formation by impairing bacterial adhesion to pipe surfaces. Other desirable design criteria include use of a distribution loop, an absence of multiple branching and dead-ended pipes, and the use of simple wall outlets with the shortest possible fluid path and a minimum of pipe fittings.

A.5 Rationale for the specific tests required by this standard

A.5.2.1 Water bacteriology

The low total viable microbial counts permitted under the provisions of this standard require that sensitive culturing methods be used. The membrane filter technique is particularly suited for this application because it permits large volumes of water to be assayed (Bland 1995). Since the membrane filter technique may not be readily available in clinical laboratories, the spread plate assay can be used as an alternative (Bland 1995). However, if the spread plate assay is used, this standard prohibits the use of a calibrated loop as the means of applying sample to the plate. This prohibition is based on the low sensitivity of the calibrated loop. A standard calibrated loop transfers 0.001 mL of sample to the culture medium, so that the minimum sensitivity of the assay is 1000 CFU/mL. This sensitivity is unacceptable when the maximum allowable limit for microorganisms is 200 CFU/mL. Therefore, when the spread plate method is used, a pipette must be used to place 0.1 to 0.5 mL of water on the culture medium.

During the evolution of this standard, there has been a continuing discussion within the committee regarding the most appropriate culture medium and incubation conditions to be used for determining total viable microbial counts. Nutrient-rich media, such as blood agar and chocolate agar, are too rich for growth of the fastidious organisms found in water, and their use is specifically prohibited by this standard. The original clinical observations on which the microbiological requirements of this standard were based used standard methods agar (SMA), a medium containing relatively few nutrients (Favero *et al.* 1974). In later versions of this standard, the use of tryptic soy agar (TSA), a general-purpose medium for isolating and cultivating fastidious organisms, was recommended because it was thought to be more appropriate for culturing bicarbonate-containing dialysate. However, several studies have shown that the use of nutrient-poor media, such as R2A or tryptone glucose extract agar (TGEA), results in an increased recovery of bacteria from water (Ledebo and Nystrand 1999; van der Linde *et al.* 1999; Pass *et al.* 1996; Reasoner and Geldreich 1985). The original standard also specified incubation for 48 hours at 35 to 37° C before enumeration of bacterial colonies. Extending the culturing time up to 168 hours and using incubation temperatures of 23 to 28° C has also been shown to increase the recovery of bacteria (Ledebo and Nystrand 1999; Pass *et al.* 1996; Reasoner and Geldreich 1985). On the basis of these results, some committee members felt that a change in culture medium and/or culturing conditions was warranted. However, other investigators have not found such clear-cut differences between culturing techniques (Arduino *et al.* 1991a; Arduino *et al.* 1991b). Moreover, culturing systems based on TSA are readily available from commercial sources, whereas those based on media, such as R2A, are not. After considerable discussion, the committee could not reach a consensus regarding changes in the assay technique, and the use of TSA or equivalent for 48 hours at 35 to 37° C remains the recommended method.

Users and manufacturers of water purification and distribution systems should recognize, however, that the culturing conditions required by this standard may underestimate the bacterial burden in the water and fail to identify the presence of some organisms. Specifically, the recommended method may not detect the presence of various nontuberculous mycobacteria that have been associated with several outbreaks of infection in dialysis units (Bolan *et al.* 1985; Lowry *et al.* 1990). Also, the recommended method will not detect fungi and yeast, which have been shown to contaminate water used for hemodialysis applications (Klein *et al.* 1990). Finally, biofilm on the surface of pipes may hide viable bacterial colonies, even though no viable colonies are detected in the water using sensitive culturing techniques (Man *et al.* 1998). Many disinfection processes poorly remove biofilm, and a rapid increase in the level of bacteria in the water following disinfection may indicate significant biofilm formation. Therefore, although the results of microbiological surveillance obtained using the test methods outlined in this standard may be useful in guiding disinfection schedules and in demonstrating compliance with the provisions of 4.2.1, they should not be taken as an indication of the absolute microbiological purity of the water.

A.5.3.2 Materials compatibility

During the 2000 revision of this standard, the FDA argued that the biocompatibility tests outlined in the *United States Pharmacopeia* (see 2.5) were not useful for water purification equipment because they were not sensitive enough to detect the presence of small amounts of toxin in large volumes of water. The FDA proposed that the *United States Pharmacopeia* biocompatibility tests be replaced by leach testing and measurement of total organic carbon in the leachate. After discussion, the committee rejected this proposal because there was no clinical outcomes data suggesting a change was necessary and because no standardized methodology for such leach testing was available.

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