List of Titles

American National Standard

ANSI/AAMI RD61:2000

Concentrates for hemodialysis

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 RD61:2000
(Partial revision of ANSI/AAMI RD5:1992)

Concentrates for hemodialysis

Developed by
Association for the Advancement of Medical Instrumentation

Approved 7 June 2000 by
American National Standards Institute, Inc.

Abstract: This AAMI standard specifies manufacturing, labeling, and testing requirements for concentrates to be diluted for use as dialyzing fluids in hemodialysis.

Keywords: hemodialysis, concentrates, dilution, dialyzing fluids, dialysate

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AAMI Standard

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Published by

Association for the Advancement of Medical Instrumentation
1110 N. Glebe Rd., Suite 220
Arlington, VA 22201-4795

Printed in the United States of America

ISBN 1–57020–140–4

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Association for the Advancement of Medical Instrumentation

Renal Disease and Detoxification Committee

This standard was developed by the AAMI Concentrates for Hemodialysis Working Group under the auspices of AAMI's 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 AAMI standard does not constitute endorsement by the federal government or any of its agencies.

Acknowledgment

The committee gratefully acknowledges the contributions of the late James T. Boag, AAKP, whose input and assistance contributed to the development of this document.

Foreword

This voluntary standard was developed by the AAMI Concentrates for Hemodialysis Working Group under the auspices of the AAMI Renal Disease and Detoxification Committee.

The American National Standard *Hemodialysis systems* was first approved in May 1981 and was published under the designation ANSI/AAMI RD5:1981. In 1996, during the 5-year review of RD5:1992, 2ed, the 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. Therefore, this standard designated as ANSI/AAMI RD61:2000 is the first of three documents that, collectively, will supersede ANSI/AAMI RD5:1992.

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.

ANSI/AAMI RD61:2000 is addressed primarily to manufacturers of concentrates. Throughout the standard, recommendations are made to use AAMI-quality water. Therefore, it would be best to review ANSI/AAMI RD62:200X,[*] *Water treatment equipment for hemodialysis applications,* along with this standard.

Concentrates for hemodialysis does not cover the dialysate that is used to dialyze patients. The making of dialysate involves the proportioning of concentrate and water at the bedside. Although the label requirements in this standard require that the water meet the requirements of ANSI/AAMI RD62:200X, *Water treatment equipment for hemodialysis applications*, there is no way for a manufacturer to evaluate that the water used to dilute the concentrate and the equipment were sufficiently maintained and operated to produce a satisfactory dialysate. The use of the concentrates to produce dialysate remains the responsibility of the dialysis facility.

In addition, this standard does not cover hemodialysis equipment, which will be addressed in a new edition of RD5, still under development. In the interim, readers should refer to ANSI/AAMI RD5:1992 for equipment requirements and/or to draft revisions of RD5 available from AAMI.

As used within the context of this standard, "shall" indicates requirements to be followed strictly in order to conform to the standard; "should" indicates that among several possibilities, one is recommended as particularly suitable, without mentioning or excluding others, that a certain course of action is preferred but not necessarily required, or that (in the negative form) a certain possibility or course of action is undesirable but not prohibited; "may" is used to indicate that a course of action is permissible within the limits of the standard; "can" is used as a statement of possibility and capability; "must" is used only for those situations which cannot be otherwise, as in the example "Monday must follow Sunday."

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 voluntary standard was 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 Road., Suite 220, Arlington, VA 22201-4795.

[*] AAMI expects to publish this standard in June 2001 following completion of appropriate approval processes.

Concentrates for hemodialysis

1 Scope

1.1 General

For the purpose of this standard, “concentrates” are a mixture of chemicals and water, or a mixture of chemicals in the form of dry powder, that are delivered to the end user to make dialysate used to perform dialysis. This standard is addressed to the manufacturer of such concentrates. In several instances in this standard, it became necessary to address the dialysate, which is made by the end user, to help clarify the requirements for manufacturing concentrates. Because the manufacturer of the concentrate does not have control over the final dialysate, any reference to dialysate is for clarification and is not a requirement on the manufacturer. The requirements established by this standard will help ensure the effective, safe performance of hemodialysis concentrates and related materials.

1.2 Inclusions

This standard includes acetate, bicarbonate, and acid concentrates in both liquid and powder forms. Also included are additives commonly called “spikes” of one or more chemicals added to the concentrate standard formula to increase the concentration of one or more specific ions in the concentrate.

1.3 Exclusions

Excluded from the scope of this standard are sorbent dialysate regeneration systems that regenerate and recirculate small volumes of the dialysate. Although references to dialysate appear herein, this standard does not address dialysate as made by the end user. This standard does not cover user-owned storage systems. Also excluded from the scope of this standard are requirements for the monitoring frequency of water purity used for the making of dialysate by the dialysis facility. The recommendations of this committee for monitoring water quality are contained in ANSI/AAMI RD62:200X,[1)] *Water treatment equipment for hemodialysis applications*. Also, this standard does not address bags of sterile peritoneal dialyzing fluids, which are drug products.

2 Normative references

The following standards contain provisions that, through reference in this text, constitute provisions of this standard. At the time of publication, the editions indicated were valid. All standards are subject to revision, and parties to agreements based on this standard are encouraged to investigate the possibility of applying the most recent editions of the standards indicated below. The Association for the Advancement of Medical Instrumentation maintains a register of currently valid AAMI/American National Standards.

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

2.2 ASSOCIATION FOR THE ADVANCEMENT OF MEDICAL INSTRUMENTATION. American National Standard, *Hemodialyzers* (ANSI/AAMI RD16:1996). Arlington (Vir.): AAMI, 1996.

2.3 ASSOCIATION FOR THE ADVANCEMENT OF MEDICAL INSTRUMENTATION. *Water treatment equipment for hemodialysis applications* (ANSI/AAMI RD62:200X). Arlington (Vir.): AAMI, 200X.

2.4 U.S. ENVIRONMENTAL PROTECTION AGENCY. *Methods for Chemical Analysis of Water and Waste* (EPA-600-4-79-020). Cincinnati (Ohio): Environmental Research Center, Environmental Monitoring and Support Laboratory, 1979 (Revised March 1983).

2.5 UNITED STATES PHARMACOPEIA. *United States Pharmacopeia-National Formulary* (USP 24-NF 19). Rockville (Md.): United States Pharmacopeial Convention Inc., 2000.

[1)] AAMI expects to publish this standard in June 2001 following completion of appropriate approval processes.

3 Definitions and abbreviations

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

3.1 acetate concentrate: A concentrated solution of salts that may contain dextrose (sometimes referred to as glucose), which, when diluted with water, yields dialysate for use in dialysis. Sodium acetate is normally used as the buffer. This concentrate is used as a single concentrate.

3.2 acetate dialyzing fluid: Dialyzing fluid without bicarbonate, using acetate as a substitute for the bicarbonate buffer.

NOTE—Acetate dialyzing fluid is generally produced from a single concentrate. Acetate is metabolized by the patient to produce bicarbonate.

3.3 acid concentrate: An acidified concentrated solution of salts that may contain dextrose (sometimes referred to as glucose), which, when diluted with water and bicarbonate concentrate, yields dialysate for use in dialysis.

3.4 anions: Ions carrying a negative charge.

3.5 batch system: Apparatus in which the dialysate is prepared prior to each dialysis session.

3.6 bedside station: A dialysate and hemodialysis circuit handling unit without a concentrate proportioning system; may monitor flow and temperature; controls dialysate pressure or ultrafiltration rate.

3.7 bicarbonate concentrate: A concentrated solution of sodium bicarbonate that, when diluted with water and acid concentrate, makes dialysate used for dialysis. Some bicarbonate concentrates also contain sodium chloride.

3.8 bicarbonate dialyzing fluid: Dialyzing fluid containing physiological or higher concentrations of bicarbonate.

NOTE—Bicarbonate dialyzing fluid is generally produced from two concentrates: one containing bicarbonate and the other containing acid and other electrolytes.

3.9 bulk delivery: The delivery of large volumes of concentrate in which the product is transferred (pumped) from the delivery container to a user's storage tank. Bulk may include containers such as 55-gallon drums, which are pumped into a storage tank maintained at the user's facility.

3.10 cations: Ions carrying a positive charge.

3.11 chlorine, combined: Chlorine that is chemically combined, such as in chloramine compounds.

NOTE—There is no direct test for measuring combined chlorine, but it can be measured indirectly by measuring both total and free chlorine and calculating the difference.

3.12 chlorine, free: Dissolved molecular chlorine.

3.13 concentrate generators: A system where the concentrate is delivered to the consumer as a powder in a single-use container and then converted into a concentrated solution by the dialysis delivery machine. This solution is used by the delivery system to make the final dialysate delivered to the dialyzer.

3.14 dialysate: An aqueous fluid containing electrolytes and usually dextrose that 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. Phrases such as "dialyzing fluid" or "dialysis solution" may be used in place of dialysate. It does not include peritoneal dialysis fluid.

3.15 dialysate supply system: Devices that prepare dialysate on line from water and concentrate or that 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 and 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.

3.16 electrolyte: Any ion or solution of ions capable of transferring or exchanging electrons. In dialysis fluid, it is the charged ions resulting from dissociation of salts when dissolved in the water.

3.17 EU: Endotoxin units as assayed by the *Limulus* Amebocyte Lysate (LAL) method when testing for endotoxins. Because endotoxins differ in their activity on mass basis, their activity is referred to a standard *E. coli* endotoxin. The current standard (EC6) is prepared from *E. coli* 0:113:H10. The relationship between mass of

endotoxin and its activity varies with both the lot of LAL and the lot of control standard endotoxin that is used. Since standards for endotoxin were harmonized in 1983 with the introduction of EC5, the relationship between mass and activity of endotoxin has been approximately 10 EU/ng.

3.18 LAL: *Limulus* Amebocyte Lysate

3.19 manufacturer: The vendor whose name appears on the label of the device; bears the responsibilities addressed to the "manufacturer" in this standard. This may be either the company that makes the device or the distributor that distributes the device.

3.20 microbial: Term referring to microscopic organisms, bacteria, fungi, and so forth.

NOTE—The term bacteriology refers to the area of study within microbiology that deals with bacteria.

3.21 nonpyrogenic: Containing ≤ 5 EU/mL of 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.

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

3.23 pyrogen: Fever-producing substance.

NOTE—Pyrogens are most often lipopolysaccharides of gram-negative bacterial origin.

3.24 spike: A small amount of a single chemical used to increase a constituent(s) in the concentrate for a single patient's treatment.

3.25 sterile: Free from all living organisms and viable spores, within the limits of tests for sterility, and maintained in that state by suitable means.

3.26 storage tank: A large tank at the user's facility for storage of concentrate from bulk deliveries.

3.27 USP: *United States Pharmacopeia-National Formulary* (USP 24-NF 19), the current version of this official compendium. (see 2.5)

3.28 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.

4 Requirements

NOTE—The term "labeling" in this standard includes any written material accompanying the hemodialysis concentrates or any written instructions provided by the manufacturer.

4.1 Labeling and documentation requirements

The label on the concentrate container shall provide the following applicable information at a minimum:

4.1.1 General labeling requirements for concentrates

a) Name and address of the manufacturer/distributor.

b) The date of manufacture.

c) An identifying lot number.

d) The composition, including for each ingredient the metric weight per volume for liquid concentrate or the weight per container of each ingredient for powder.

e) For batch systems, the volumes of dialysis concentrate and water that shall be mixed.

f) For proportioning systems, the ratio of dialysis concentrate and water that shall be mixed.

g) The trade name of the product.

h) A statement on storage requirements such as "Store at or below room temperature. Do not freeze." And/or "Short-term exposure to warm conditions (40 °C) will not harm acid concentrate."

i) Any special requirements that may be necessary because of the specificity of the product (i.e., the use of concentrate generators with a specific dialysis delivery system).

j) A warning stating that bacterial growth may occur when using bicarbonate concentrate (bicarbonate concentrate only); any other cautions or warnings that must be taken in the mixing of the concentrate.

k) A statement to test the final dialysate for conductivity and pH.

l) A statement that AAMI-quality water meeting the requirements of ANSI/AAMI RD62:200X, *Water treatment equipment for hemodialysis applications,* shall be used to dilute the concentrate to make dialysate.

4.1.2 Labeling requirements for liquid concentrate

a) The expiration date of liquid concentrate, if appropriate. Manufacturers of liquid concentrates should have data supporting the expiration date.

b) The composition of the dialysate, including the nominal concentration of each electrolyte in the dialysate in millequivalents per liter (mEq/L); and the concentration of nonelectrolytes in the final diluted solution in milligrams per deciliter (mg/dL). For bicarbonate concentrate, the chemical concentration of the final dialysate need not be included on the label; this information is on the acid concentrate label.

c) A statement that the solution is nonpyrogenic, if applicable.

d) The fill volume of the container.

e) The dilutional effects on the final dialysate of any liquid spikes (labeling on liquid spikes only).

f) The nominal conductivity of the final dialysate when mixed according to the manufacturer's instructions or a statement that such information is available from the manufacturer.

4.1.3 Labeling requirements for powder concentrate

a) For concentrate generators, the proportioning system or dialysis machine they are to be used with.

b) The length of time a concentrate generator can be expected to function and provide concentrate to the machine.

c) For powder concentrates, the amount of water that must be used to reconstitute the concentrate.

d) For bicarbonate concentrate, the time limit for use in order to prevent possible bacterial contamination. Also, appropriate warnings that residual bicarbonate concentrate, uncleaned mixing tanks, and mixing systems will support bacterial growth.

e) For powder concentrates, the water quality that should be used to mix the concentrate (i.e., the maximum bacterial and endotoxin levels).

4.1.4 Aqueous concentrate

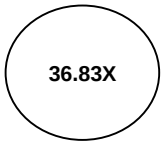
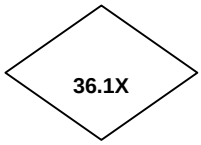
The label shall include the instructions to mix thoroughly prior to use (this is particularly important after freezing) and instructions not to use damaged containers. When bicarbonate is used, a warning shall be included noting that bacterial growth may occur in concentrated or diluted bicarbonate solutions.

The labeling shall state that once opened, the bicarbonate concentrate shall be used within the time limit specified by the manufacturer, or within 24 hours, unless measures to extend that limit are documented. The time limit for use (determined by the manufacturer) shall be the period during which the concentrate consistently produces a dialysate that meets the chemical and microbiologic requirements of this standard when used in a properly maintained system and mixed with water that meets the ANSI/AAMI RD62:200X, *Water treatment equipment for hemodialysis applications* standard.

Means shall be provided to readily distinguish between solutions (acetate, bicarbonate, and their acid counterpart solutions) and their appropriate proportioning ratios. Labels shall be white for acetate, blue for bicarbonate, and red for acid concentrate. Each container shall display a geometric symbol as the shape of the label or another easily visible form. Symbols shall be a circle for 36.83X, a square for 35X, triangle for 45X, and a diamond for 36.1X. A distinctive geometric shape will be used for any other dilution ratio. The number representing the proportioning system should also be easily visible and located within the boundaries of the geometric symbol on acid concentrate (see Table 1).

Table 1—Symbols for bicarbonate dialysis concentrate container system

CONCENTRATE TYPES

Designation					Other[a] (New)
Mix Ratio[b]	1:1.23:32.77 35	1:1.83:34 36.83	1:1.72:42.28 45	1:1.1:34 36.1	TBD[a]
Acid Mix Ratio[c]	1:34	1:35.83	1:44	1:35.1	TBD[a]
Bicarbonate Mix Ratio[d]	1:27.6 (84 g/L)	1:19.1 (65.95 g/L)	1:25.1 (81.25 g/L)	1:31.8 (saturated)	TBD[a]
AAMI Symbol	SQUARE	CIRCLE	TRIANGLE	DIAMOND	TBD[a]

[a] Any new ratio that does not fit the above matrix should be designated with a unique geometric symbol with the ratio contained in the symbol.

[b] Acid : Bicarbonate : Water

[c] Acid : Water + Bicarbonate Concentrate

[d] Bicarbonate : Acid + Water

4.1.5 Dry concentrate

The label shall include recommended storage conditions and mixing precautions. When bicarbonate is used, microbial limits for water used and other microbial concerns (e.g., disinfection of mixing and storage apparatus) shall be addressed. Instructions for dry bicarbonate concentrate that is intended to be mixed on-site shall state that bicarbonate concentrates prepared on-site must meet the microbiologic requirements specified in 4.2.4 and 4.2.11 and must be labeled to be used within a period of time demonstrated to reliably meet the requirements of 4.2.4 and 4.2.11. Where necessary to ensure quality of the product by the end user, directions shall instruct the user on the proper use of the product. Such directions shall include, but not be limited to: the quality of water to be used to dissolve the dry powder, the correct testing method to ensure proper dilution (e.g., conductivity or pH) of the final dialysate, and any specific precautions that must be followed to ensure proper use of the product.

As noted in 4.1.4 and in Table 1, for liquid concentrate, means shall be provided to distinguish readily between dry concentrates (acetate, bicarbonate, and their acid counterparts) and their appropriate proportioning ratios. Labels shall be white for acetate, blue for bicarbonate, and red for acid concentrate. Each container of concentrate intended for proportioning systems shall display a geometric symbol as part of the label or another easily visible form. Symbols shall be a square for 35X, a circle for 36.83X, a triangle for 45X, a diamond for 36.1X, and a distinctive geometric shape that differentiates the product for any other dilution ratio. The numbers representing the proportioning system should also be easily visible and located within the boundaries of the geometric symbol.

4.2 Requirements for the concentrate

4.2.1 Physical state

The concentrate for hemodialysis may be supplied in dry and/or aqueous form. Packaging shall be either for single-patient use or for multiple-patient (bulk) use.

4.2.2 Solute concentrations

4.2.2.1 Liquid solute concentrations

All electrolytes identified on the label shall be present within ± 5 % or ± 0.1 mEq/L, whichever is greater, of the stated concentration, with the exception of sodium, which shall be present within ± 2.5 % of the labeled concentration. Because the chloride levels depend on several other electrolytes, no tolerance is assigned to the chloride. Dextrose shall be present within ± 5 % or ± 5 mg/dL, whichever is greater, of the labeled concentration.

4.2.2.2 Powder weights

When concentrate is packaged in dry form and is mixed according to the manufacturer's instruction for use, the final concentrate shall meet the specifications in 4.2.2.1.

4.2.3 Water quality

The quality of water used in the manufacture of the concentrate shall be in accordance with ANSI/AAMI RD62:200X, *Water treatment equipment for hemodialysis applications*. The maximum contaminant levels are included in annex B of this standard.

4.2.4 Bacteriology

Concentrate containing bicarbonate supplied as a liquid must be provided in a sealed container and must contain no more than 200 CFU/mL at the end of the manufacturer's recommended shelf life.

4.2.5 Fill volume

The fill volume of a liquid single-use container for use with batch systems shall be within 2 % of the labeled volume. For nonbatch systems, the fill volume shall be greater than 97 % of the stated volume.

4.2.6 pH

When acetate concentrate is diluted as directed on the label, with appropriate water, the resulting dialysate should have a pH in the range of 7.0 to 7.6 and shall require less than 1 mEq of acid or base to titrate one (1) liter to a pH of 7.4.

4.2.7 Chemical grade

All chemicals shall meet the requirements of the current *United States Pharmacopeia-National Formulary,* including all applicable portions of the General Notices and of the General Requirements for Tests and Assay. If all other requirements are met, monograph limits for sodium, potassium, calcium, magnesium, and/or pH may be exceeded provided that correction is made, if necessary, for the presence of those ions in the final formulation. Also, the USP labeling requirements that specify labeling for use in hemodialysis need not be complied with if the manufacturer is performing its own testing to meet the USP requirements.

4.2.8 Particulates

The aqueous dialysate concentrate shall be filtered through a 1.2-micron or finer particulate filter. The particulate filter used shall have a non-fiber-releasing membrane that does not contain material of known potential for human injury.

4.2.9 Additives

All ingredients in the final concentrate shall be listed on the label.

4.2.10 Containers

Containers, including the closures, shall not interact chemically or physically with their contents in any manner to alter the strength, purity, or quality of the concentrate during handling, storage, and shipment. The containers shall have closures that prevent contamination or loss of content. Each container shall be marked with the appropriate color and symbol to indicate its contents (see 4.1.4 and 4.1.5).

4.2.11 Pyrogenicity

The concentrate shall be shown to be nonpyrogenic, or the concentrate shall be formulated and labeled specifically for use with a process that will produce a nonpyrogenic solution. Alternatively, the chemicals and water used to manufacture dialysate concentrate shall be shown to be nonpyrogenic, and the manufacturing process shall be appropriately validated. If the LAL assay is used, maximum endotoxin shall not exceed 2 EU/mL. When testing powder, the endotoxin level shall not exceed 2 EU/mL when properly mixed with water.

4.2.12 Bulk delivered concentrate

When concentrate is delivered in bulk form, the responsible person for ensuring compliance with the section below shall be defined by the legal point of transfer of the shipment. Once the concentrate is transferred from the manufacturer to the user, it becomes the user's responsibility to maintain the product in a usable state.

When concentrate is delivered to the end user in bulk form, the user shall take precautions to ensure the correct formulation is delivered to the correct storage tank. Written documentation of the correct deliveries and the point of transfer of responsibility shall be made. If the concentrate is delivered in 55-gallon drums, it is the end user's responsibility to ensure that the correct formula is used according to the patient's prescription.

If the concentrate is pumped into a user's storage tank, adequate procedures and training should be in place at the user's facility to ensure:

a) No mixing of different formulas will occur in the tanks.

b) Adequate cleaning and sanitization procedures exist to ensure the quality and integrity of the stored concentrate.

c) Adequate and appropriate labeling of the stored and dispensed concentrate exists for lot number, formula dilution factor, storage conditions, and closure of the container.

4.2.13 Concentrate generators

Concentrate generators include systems that mix powder into a concentrate by forming a slurry or concentrated solution in a container specifically designed to function with one manufacturer's dialysis machine. Mixing could be accomplished either by an automated system within the delivery system or by a manual mixing system. Because the concentrate is delivered to the user as a powder in a container designed for a specific machine, it is the concentrate manufacturer's responsibility to ensure that:

a) All applicable sections of this document dealing with powder are met.

b) The container will function with the machine as defined by the manufacturer of the machine.

c) The labeling shall clearly indicate the machines for which the concentrate generator is intended.

d) The amount of time is indicated that the container can reasonably be expected to provide solution to the dialysis machine.

e) Any additional information is provided that must be known by the user to ensure that the product will be used correctly (e.g., water quality, shelf life after mixing, etc.).

Concentrate generators can be used in either 36.1X or 45X systems. The concentration of the sodium bicarbonate out of the concentrate varies throughout the treatment. The dialysis machine measures the conductivity and continually adjusts the amount of bicarbonate concentrate feed into the dialysate stream. Because concentrate generators can be used with either 36.1X or 45X machines, the committee decided not to label them with a special symbol but rather to label the machine they are to be used with. This places on the user the burden to ensure that the dialysis machine is properly set-up and that the correct concentrates are being supplied.

It is the machine manufacturer's responsibility to design and manufacture the dialysis machine according to the AAMI/ANSI equipment standard, including design, construction, and all necessary safety checks, to ensure that the system will deliver a safe and effective dialysate to the dialyzer. Where necessary, filtering shall be provided by the manufacturer to prevent undissolved powder from entering the dialysate stream.

4.3 Manufacturing equipment

Any material components of the manufacturing equipment (e.g., piping, storage, and distribution systems) that have contact with the final concentrate or any component of the concentrate shall not interact physically or chemically with the fluid so as to significantly alter the strength, purity, or quality of the concentrate delivered to the end user.

5 Tests

Clause 5 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. 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 validation of the test method is demonstrated.

5.1 Labeling and documentation requirements

Compliance with the labeling requirements of 4.1.1 can be determined by inspection.

5.2 Testing to meet the requirements for the concentrate

5.2.1 Physical state

Compliance with the requirements of 4.2.1 can be determined by visual inspection.

5.2.2 Solute concentrations

Compliance with the requirements of 4.2.2 for calcium, potassium, magnesium, and sodium can be determined by using methods referenced in the American Public Health Association's *Standard Methods for the Examination of Water and Wastewater* and/or the U.S. Environmental Protection Agency's *Methods for Chemical Analysis of Water and Waste*, and/or other equivalent analytical methods. Samples shall be collected in sealed bottles and diluted to dialysate. Appropriate containers and pH adjustments shall be used to ensure accurate determinations. Refer to Table B.2 for complete details.

Compliance with the requirements for the contents of the dialysate can also be determined as follows:

a) *Potassium:* flame photometry method, atomic absorption (direct aspiration), or ion-specific electrodes;

b) *Acetate:* gas chromatography, liquid chromatography, or enzymatic methods;

c) *Dextrose:* polarimetry, enzymatic, or chemical methods;

d) *Bicarbonate:* acid titration and calculation or other method for total CO_2;

e) *Calcium:* EDTA titrimetric method, or atomic absorption (direct aspiration), or ion-specific electrodes;

f) *Magnesium:* atomic absorption (direct aspiration);

g) *Sodium:* atomic absorption (direct aspiration), flame photometric method, or ion-specific electrode.

5.2.3 Water Quality

Compliance with the water quality requirements of 4.2.3 can be determined by using methods referenced in the American Public Health Association's *Standard Methods for the Examination of Water and Wastewater* (2.1) and/or the U.S. Environmental Protection Agency's *Methods for Chemical Analysis of Water and Waste* (2.4), and/or other equivalent analytical methods. Samples shall be collected at the entrance of water to the concentrate manufacturing system. Appropriate containers and pH adjustments shall be used to ensure accurate determinations.

For reference, the maximum contamination levels are contained in annex B. Also refer to ANSI/AAMI RD62:200X, *Water treatment equipment for hemodialysis applications*.

5.2.4 Bacteriology

The following procedure should be used to determine compliance with the requirements of 4.2.4. Total viable counts (standard plate counts) shall be obtained using the membrane filter technique. Commercial water testing devices or spread plates may also be used. The calibrated loop technique shall not be used. Culture media should be trypticase soy agar (TSA) or equivalent. Blood agar and chocolate agar shall not be used. Incubation is at 35 °C to 37 °C, and colonies shall be counted after a minimum of 48 hours of incubation. The total viable count should not exceed 200 CFU/mL. All rinse water and dilution blanks used in the assay must be with 0.9 % normal saline or other properly validated rinse solution.

5.2.5 Fill volume

Compliance with the requirements of 4.2.5 can be determined by the use of appropriate volumetric or gravimetric techniques.

5.2.6 pH

The pH of the dialysate can be determined by using volumetric techniques to obtain appropriate dilution of the concentrate and by measuring the pH with a glass electrode.

5.2.7 Chemical grade

Purity of chemicals can be determined by test methods outlined in the *United States Pharmacopeia-National Formulary.*

5.2.8 Particulates

Compliance with the requirements of 4.2.8 can be determined by inspection of the manufacturing records of the product to ensure that the concentrate was filtered through a 1.2-micron filter.

5.2.9 Additives

Compliance with the requirements of 4.2.9 can be determined by inspection of the manufacturing records of the product or final product analysis.

5.2.10 Containers

Compliance with the requirements of 4.2.10 can be determined by the tests for plastic containers as described in the *United States Pharmacopeia-National Formulary* such as USP Class VI or leach testing with chemical analyses of the extractable.

5.2.11 Pyrogenicity

Compliance with the requirements of 4.2.11 can be determined by *United States Pharmacopeia-National Formulary* rabbit test or the LAL test for endotoxins.

5.3 Manufacturing equipment

The biocompatibility of material components used in the manufacturing equipment should be determined by verifying that the components in contact with the concentrate or water are unreactive materials (e.g., plastics) meeting the requirements of 5.2.10 or appropriate stainless steel, and that these components are not known to cause toxicity in dialysate systems (examples of materials that should NOT be used in manufacturing equipment include copper, brass, galvanized material, or aluminum).

Annex A
(informative)

Rationale for the development and provisions of this standard

A.1 Introduction

The items included within the scope of this standard are the reagents and devices required to prepare dialysate and dialysate concentrate. This standard addresses both liquid and dry concentrates. It is addressed primarily to manufacturers but has useful information for the user.

Systems that regenerate dialysate by passing the dialysate through systems to restore the dialysate's original content have been specifically excluded from the scope of this standard.

The development of a hemodialysis systems standard that precedes this concentrate standard began in the late 1960s as a collaborative effort between the American Society for Artificial Internal Organs and the Association for the Advancement of Medical Instrumentation. The hemodialysis systems standard RD5:1982, *Hemodialysis systems*, was first published in 1982 as an industry standard.

The AAMI Renal Disease and Detoxification Committee initiated a thorough review of the 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 had become common. Task groups were established in those areas that the committee felt needed most careful review, including bicarbonate dialysis, ultrafiltration rate (UFR) controls, monitors, and microbiological aspects. As a result of the work of these task groups and review by the full committee, a 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. During the 1992 revision of the document, the committee concluded that based on available data, the introduction of highly permeable membranes did not require the establishment of new limits on pyrogens in water for dialysis. During the drafting of the 1997 revisions, the committee added to the standard maximum levels for both endotoxin and microbiological contamination. The allowable levels of chemical contaminants in water acceptable for hemodialysis were not changed. At this time the committee decided to divide the standard into several sections. The proposal was to have three documents which would replace the existing hemodialysis systems standard. The three standards would address concentrate, water for hemodialysis, and hemodialysis equipment.

The current rewriting of the hemodialysis concentrate standard took into consideration new developments over the preceding 5 years. The major changes included were the addition of an endotoxin standard; the inclusion of new methods of developing concentrate such as powder concentrate generators, which are built into the dialysis machine; the bulk delivery of concentrate; and a total restructuring 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 Limitations of the standard

Concentrate solutions for use in preparing hemodialysis dialyzing solutions (dialysate), whether liquid or dry, whether general or specific, are put into use by a professional user; this critical final step is not under the control of the manufacturer. This two-stage responsibility may produce confusion as to the duties and liabilities of the parties involved.

The concentrate, properly manufactured and labeled, may be used in erroneous combinations; the correct option may not be used for a given patient; improper handling may lead to contamination of the final dialysate. No equipment or system can prevent or avoid these errors. Only an informed and reliable clinical professional can control these final steps in the process. The potential for human error requires human oversight.

These circumstances necessitate that the manufacturer labels the concentrate clearly, completely, and explicitly, and documents the delivery of the product and transfer of responsibility for its application to the user facility and its professional staff. These circumstances also require the AAMI committee to assemble and make accessible clear, direct, and logical information for the users of hemodialysate concentrate so that they may responsibly carry out treatment using these products in appropriate systems for appropriate patients under appropriate safeguards. To that end, the AAMI Renal Disease and Detoxification Committee advises the user to view the standard also as a

guideline, while recognizing that this standard is primarily addressed to the manufacturer of the concentrate purchased by the user.

A.3 Need for the standard

This standard seeks to prevent the use of options that are hazardous to patients treated with hemodialysis systems. Examples of the need for the standard are 1) the potential for poisoning because of formulation of dialysate with water containing high levels of certain contaminants; and 2) dangerous treatment because of use of the wrong concentrates.

While the principal concern of the committee was for adequate, safe treatment of the patient, other considerations have influenced the standard such as theoretical hazards, or remote short- or long-term risks. Hemodialysis is a complicated and expensive procedure. The cost of treating end-stage renal disease patients, much of which goes toward hemodialysis, exceeds ten billion dollars per year. This standard must thus address prudence, efficiency, and cost effectiveness to be applicable.

The committee, therefore, has attempted to set standards that are consistent with cost constraints and operator 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 operator. More liberal standards have been chosen when the risk to the patient is low or when a large safety factor approaches the limits of available instruments, requires expensive modifications, or poses significant problems for the operator.

A.4 Rationale for the specific provisions of this standard

A.4.1 Labeling and documentation requirements

Existing federal regulations establish general requirements for the labeling of all medical devices, including information such as name and address of manufacturer and lot number. The committee decided, 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 sections 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.

A.4.2 Concentrate for hemodialysis

The display of identification data and basic content information provides necessary information for use and reference and ensures traceability. Although the Keshaviah report (1980) recommended that the size distribution of particulates in the finished product be disclosed, the committee disagreed with the recommendation, which would require sampling of each batch for particulates and disclosure of results on the label. The committee took this position because disclosure of the numbers of particulates would have no practical meaning to the user and because no limits on particulates have been established. Bicarbonate dialysate requires two concentrates to be used in preparing dialysate because concentrated calcium and bicarbonate will precipitate if combined. Technology for dual proportioning is widely available. Different systems proportion at different ratios (e.g., 35X, 36.83X, 45X), and other systems directly use dry powder. Some of these concentrates contain sodium chloride in the bicarbonate solution, requiring a corresponding adjustment in the parallel counterpart acid concentrate. This complicated assortment can lead to confusion. Adequate monitoring does not currently exist to ensure that mismatched concentrates do not produce a final dialysate of proper total conductivity but of improper composition. The user is cautioned not to rely solely on conductivity measurements to ensure safety, but to consider all relevant factors, including pH. Recognition and application of appropriate concentrates to produce the desired dialysate is the responsibility of the end user.

Standards for bicarbonate dialysate systems thus must address both proportioning and monitoring systems, as well as concentrate packaging, labeling, and connections.

In view of the potential for improper use of concentrate, the committee decided to emphasize the importance of user education and training and to specify that labels should be color coded and have distinctive shapes printed on them.

Bicarbonate dialysate can increase precipitation and scaling within the dialysate path, including on monitoring electrodes. Regular, effective dialysate path cleaning is critical to machine performance. Haloduric bacteria can multiply in bicarbonate concentrates, although no bacteria multiply in acid or acetate concentrates. Specifications for handling, shelf life, and microbiologic monitoring must be established by each user in accordance with manufacturer's recommendations. Manufacturers must provide full information and rational guidance for health professionals to produce safe, appropriate dialysate.

With present technology, the final safeguard must be a responsible operator of the equipment. To achieve this final safeguard, staff members must be trained and supervised. Such measures are the responsibility of the medical director of the dialysis program.

A.4.3 Labeling requirements for powder concentrate

The committee is aware of incidents where bicarbonate concentrate supported bacterial growth. Other data supports the fact that if containers are not properly cleaned and disinfected, residual bicarbonate concentrate will support bacterial growth. Usually a time limit is recommended by the manufacturer to minimize the occurrence of bacterial growth. This limit should be closely followed by the user.

The committee was not aware of any incidents of pyrogenic reactions caused by pyrogens in the acid part of the concentrate. During the review of this document in 1999, it was suggested that the statement in 4.1.2 c) be revised to remove the clause “if applicable.” The committee did not think this removal was appropriate because there were no reported incidents of acid concentrate causing pyrogenic reactions. There is also the possibility that acid concentrate will deactivate pyrogens because of its low pH.

A.4.4 Aqueous concentrate

This specialized information provides for the proper use of concentrate for hemodialysis supplied in an aqueous form. The committee considered requiring a precaution against excessive cold, as well as requiring a precaution against excessive heat, but it was pointed out that the stipulation for thoroughly mixing before use would protect against using concentrate that had been subjected to extreme cold. Furthermore, the committee was especially interested in preventing inadvertent use of the wrong solution caused by similarities in containers.

A.4.5 Dry dialysis concentrate

This specialized information provides for the proper use of concentrate for hemodialysis supplied in a dry form. During the 1997 revision of this standard, 4.1.3 was revised to more clearly address the manufacturer’s responsibility.

The label shall include instructions to avoid exposure to excessive temperature and to keep the container tightly sealed until use. When bicarbonate is used, a warning shall be included noting that water containing an otherwise acceptable number of bacteria will be entering an environment that can support bacterial growth and, therefore, procedures must be taken to ensure microbiologic safety. The instructions may suggest practices such as improved water quality or short holding time, and they should recommend that containers be clean and recently disinfected. The bicarbonate mixing apparatus should also be disinfected at appropriate intervals, usually before preparing each batch.

A.5 Requirements for the concentrate

A.5.1 Physical state

Concentrate may be in either aqueous or dry form, depending on the application. In some cases, a portion of the concentrate is aqueous and the remainder is in dry form; in other cases, two aqueous concentrates are used.

A.5.1.1 Solute concentrations

It is essential that the actual concentrations of the solutes contained in the concentrate be as close as possible to the labeled amount. The committee decided that, although excessive variations could be hazardous to the patient, tolerances of less than 5 % for dextrose and the minor cations cannot consistently be achieved. Further, when those components are present at low levels, a variation of 0.1 mEq/L for the minor cations or of 5 mg/dL for dextrose is acceptable. This variance is necessary to account for minor amounts of such solutes present in the other raw materials and limitations of manufacturing and testing.

Previously, this standard required sodium and chloride to be present within 2 % of the labeled concentration. The international standard (ISO 13958) has adopted a level of 2.5 %, and the committee accepts this tolerance. Chloride ion is dependent only upon the cations in concentrate and thus does not require an individual tolerance.

A.5.1.2 Water quality

The committee decided that there should be some assurance that the water used to prepare the concentrate would not significantly contribute to the chemical contaminant levels present in the concentrate itself. When the standard underwent AAMI’s mandatory fifth-year review in 1997, the water section was placed into its own standard. The requirements for water were removed from this standard and the water standard was referenced instead. Therefore, water used to prepare the concentrate must meet the water quality requirements of the AAMI water standard. It is necessary, therefore, also to comply with the water standard when using hemodialysis concentrate. The drafters of this standard thought that the water quality tables contained in the original RD5 standard should be repeated in this standard. Therefore, Tables 1 and 2 of RD5 are reprinted in annex B.

A.5.1.3 Bacteriology

Bicarbonate concentrates have been shown to support bacterial growth and to provide another source of initial bioburden capable of rapid increase after dilution (Ebben 1987; Bland 1987). Recognition of this hazard requires additional precautions in preparation, containers, storage, and prompt use to avoid excess growth of haloduric organisms. Practices to ensure safety are to be recommended by manufacturers and established and followed by users.

The committee has had considerable discussion regarding the use of appropriate media and incubation conditions to culture bicarbonate concentrate. This standard gives the method accepted by the committee. Other methods which have been shown by test results to give at least substantially equivalent results may be used in place of the reference test described in 5.2.4.

A.5.1.4 Fill volume

The supplier should ensure that the volume is consistent with the label and thus with expectations of the user.

A.5.1.5 Acidity or alkalinity

Acetate dialysate: Precise control of the pH of acetate dialysate is not possible because of the influence of the facilities' water and the lack of pH buffer in the concentrate. A pH range of 6.0 to 8.0 has been selected because it is achievable and because the committee is unaware of adverse effects resulting from use of dialysate within this range. Heparin, used as an anticoagulant in hemodialysis, rapidly loses its activity below a blood pH of 7.0 and is almost completely ineffective at a blood pH of 6.7. A correlation between extremely acidic acetate dialysate (pH as low as 5.3) and frequency of clotting has been reported. Acetate dialysate pH does not directly affect blood pH because of buffers in blood, low buffering capacity of acetate dialysate, and metabolism of acetate to bicarbonate.

Bicarbonate dialysate: Bicarbonate dialysate is a highly buffered system. The pH of bicarbonate dialysate typically ranges from 7.1 to 7.5. This pH range is stable within the usual changes in concentration of either the acid or the bicarbonate portion. pH levels outside this range can indicate a serious misproportioning of concentrates and can result in serious acid/base complications for the patient.

A.5.1.6 Chemical grade

A.5.1.6.1 Trace metals

Keshaviah et. al. (1980) suggested that contaminant levels for trace metals in the concentrate be at levels such that after diluting with water of the quality specified in Table 1, the contaminant levels of the resulting dialysate should be no greater than 10 % higher than in the water alone. They go on to suggest that if this specification cannot be met with USP grade chemicals, disclosure of the actual contaminant levels is considered appropriate. The committee finds those suggestions inappropriate for the following reasons:

1) Except for aluminum, adequate reference solutions and optimized analytical methods for measuring potential trace metal contaminants in dialysate concentrate are not available and would be expensive to develop.

2) Because materials and methods are not available, it is not possible to evaluate the need for control by sampling present products.

3) In the case of aluminum, testing of concentrates from several manufacturers by Allen Alfrey, MD, and by Travenol Laboratories of its own concentrates uniformly showed levels well below the AAMI recommended limits of 10 parts per billion (ppb) for water for dialysis.

4) Dr. Alfrey has also studied trace-element abnormalities in the tissue of dialyzed and nondialyzed uremic patients in a group of Australian patients and in two U.S. centers (Alfrey and Smythe 1978). He concluded that, with the exception of aluminum, no evidence existed in his data that dialyzed uremic patients have trace-metal tissue burdens different from those in the nondialyzed uremic controls. Increased aluminum levels were thought to probably be the result of the ingestion of aluminum-based antacids rather than a result of dialysate aluminum levels.

The committee recommends that all chemicals meet the requirements of the *United States Pharmacopeia-National Formulary*. The limits of sodium, potassium, calcium, magnesium, and pH may be excluded, provided that the exceptions are compensated for in the final formula. The committee thought that since these ions were being added to the final formula, it would be possible to make the necessary corrections to compensate for these ions without incurring the cost of meeting these limits.

The committee also considered whether chemicals to be used in hemodialysis should be so labeled. Since the labeling requirement did not reflect any change in USP specifications, the committee decided that meeting this requirement did not increase product quality.

A.5.1.6.2 Arsenic

Although the importance of controlling the arsenic level in the dialysate is undisputed, the problems regarding a suitable method for detecting arsenic levels in the concentrate at the 5-ppb level recommended by Keshaviah et al (1980) are the same as described in A.5.1.6.1 for other chemical contaminants. The USP method for arsenic is available for detection at 0.05 mg/L (50 ppb). Until a more sensitive method has been defined, the committee recommends the 0.05 mg/L level for the diluted concentrate. During the 1997 mandatory review of this standard, the committee realized that arsenic was covered by the general standards for contaminants in concentrate and removed specific reference to arsenic.

A.5.1.7 Particulates

Although Keshaviah et al (1980) recommend disclosure of particulate size distribution in the finished product, the committee disagrees with the recommendation for reasons outlined in A.4.2.

A.5.1.8 Additives

All substances in the final concentrate must be specified on the label so that the user will be able to determine the exact composition of the product, because any component of the concentrate may diffuse into the bloodstream. Preservatives or indicators present in the concentrate should be indicated on the label.

A.5.1.9 Containers

Substances from the containers that contaminate the concentrate may diffuse into the patient during dialysis and may cause harm to the patient. The committee, therefore, felt that relatively nonreactive containers that would not affect strength or purity of the concentrate should be used.

A.5.1.10 Pyrogenicity

Control of endotoxin in the concentrate is necessary to prevent pyrogenic reactions in the patient during dialysis. When this standard underwent the mandatory fifth-year review in 1997, an endotoxin limit was deemed to be appropriate because evidence was presented that with high-permeability dialyzers, it was possible for pyrogens in the dialysate to enter the patient. Therefore, a limit of less than 2 EU/mL was selected to coincide with the water standard, ANSI/AAMI RD62:200X, *Water treatment equipment for hemodialysis applications*.

A.5.1.11 Bulk delivery concentrates

The delivery of concentrate in bulk containers has become commonplace in dialysis. This practice carries with it responsibilities for both the user and the manufacturer. When bulk deliveries are made, the product is dispensed into a large holding tank and the original labeling is lost. The maintenance of the holding tank is normally the responsibility of the user. The tank and its associated piping must be periodically cleaned and disinfected according to standard procedures. Care must be taken to ensure that the correct formula is placed into the correct holding tank.

Many different ways of accomplishing bulk delivery of concentrate are used. The committee decided that the point of transfer of the concentrate solution is the point at which the responsibility for its labeling and integrity transfers to the user. Written procedures should define this exchange.

A.5.1.12 Concentrate generators

As technology progresses, some manufacturers produce concentrate preparation systems that prepare a solution for use by the dialysis machine. During the 1997 rewrite of this standard, the committee decided that such systems should be added to this standard. Those systems create a concentrated slurry that is dynamically proportioned with the acid concentrate in the dialysis machine. Because the proportioning is dynamic, these canisters can be used with several different proportioning ratio acids (36.1X and 45X). Symbols on those labels were deemed to be unnecessary and possibly confusing because of their multiple use. It was determined that the connectors could vary and thus make it necessary to tell which machine the canisters were to be used with.

A.5.2 Manufacturing equipment

Nontoxicity of construction materials for manufacturing equipment is of major importance to prevent contamination of the concentrate. Data are now available that demonstrate 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). Other materials have been documented as being hazardous to the patient (e.g., brass, zinc, iron, and aluminum), and they should also be avoided. Some well-recognized nontoxic materials include certain stainless steel formulations, silicone rubber, borosilicate glass, polypropylene, polyvinylchloride, high-density polyethylene, and polytetrafluorethylene. The hazard in construction materials derives from long-term cumulative toxicity.

When the standard underwent AAMI's mandatory fifth-year review in 1997, the committee revised the requirements of this section to address only the concentrate manufacturing system. The requirements for dialysate handling and biocompatibility were moved to the dialysis machine standard. Because this standard was addressed to the manufacturer, the committee decided that standards addressing dialysate were better addressed in a dialysate recommended practice (under development).

Annex B
(informative)

Chemical contaminant levels and tests

B.1 Introduction

The Renal Disease and Detoxification Committee of the Association for the Advancement of Medical Instrumentation originally included within the standard *Hemodialysis systems* (RD5:1992) two tables that gave the maximum contamination levels for water quality and the appropriate test methods for analyzing contaminants. The committee thought it appropriate to maintain the tables with the concentrate standard, and updated versions of the tables are set forth below. Further information on the water used to make hemodialysis concentrate can be found in the standard ANSI/AAMI RD62:200X, *Water treatment equipment for hemodialysis applications.*

Table B.1—Hemodialysis water quality: Chemical contaminant levels[a)]

Maximum allowable chemical contaminant levels in water used to prepare dialysate and concentrates and to reprocess dialyzers for multiple use.

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
Cyanide	0.02
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.

Table B.2—Analytical tests for chemical contaminants

Contaminant	Test Name	Normative Reference, Test Number[a)]
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
Cyanide	Spectrophotometric	2.3, #4500-CN^- E
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 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

[a)] Normative references are found in ANSI/AAMI RD62:200X, *Water treatment equipment for hemodialysis applications*.

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