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Concentrates for haemodialysis and related therapies

Concentrés pour hémodialyse et thérapies apparentées

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ISO copyright office
Case postale 56 • CH-1211 Geneva 20
Tel. + 41 22 749 01 11
Fax + 41 22 749 09 47
E-mail copyright@iso.org
Web www.iso.org

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

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

For an explanation on the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the WTO principles in the Technical Barriers to Trade (TBT) see the following URL: Foreword - Supplementary information

The committee responsible for this document is ISO/TC 150, *Implants for surgery*, Subcommittee SC 2, *Cardiovascular implants and extracorporeal systems*.

This third edition cancels and replaces the second edition (ISO 13958:2009), which has been technically revised.

Introduction

The requirements and goals established by this International Standard will help ensure the effective, safe performance of haemodialysis concentrates and related materials. This International 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.

Throughout this International Standard, recommendations are made to use ISO-quality water. Therefore, it is recommended to review ISO 13959 along with this International Standard.

This International Standard does not cover the dialysis fluid that is used to clinically dialyse patients. Dialysis fluid is covered in ISO 11663. The making of dialysis fluid involves the proportioning of concentrate and water at the bedside or in a central dialysis fluid delivery system. Although the label requirements for dialysis fluid are placed on the labelling of the concentrate, it is the user's responsibility to ensure proper use.

In addition, this International Standard does not cover haemodialysis equipment, which is addressed in IEC 60601-2-16:2012.

The verbal forms used in this International Standard conform to usage described in Annex H of the ISO/IEC Directives, Part 2. For the purposes of this International Standard, the auxiliary verb

— "shall" means that compliance with a requirement or a test is mandatory for compliance with this International Standard,

— "should" means that compliance with a requirement or a test is recommended but is not mandatory for compliance with this International Standard, and

— "may" is used to describe a permissible way to achieve compliance with a requirement or test.

Concentrates for haemodialysis and related therapies

1 Scope

This International Standard specifies minimum requirements for concentrates used for haemodialysis and related therapies. For the purpose of this International Standard, "concentrates" are a mixture of chemicals and water, or chemicals in the form of dry powder or other highly concentrated media, that are delivered to the end user to make dialysis fluid used to perform haemodialysis and related therapies. This International Standard is addressed to the manufacturer of such concentrates. In several instances in this International Standard, it became necessary to address the dialysis fluid, 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 dialysis fluid, any reference to dialysis fluid is for clarification and is not a requirement of the manufacturer.

This International Standard includes concentrates in both liquid and powder forms. Also included are additives, also called spikes, which are chemicals that may be added to the concentrate to increase the concentration of one or more of the existing ions in the concentrate and thus in the final dialysis fluid. This International Standard also gives requirements for equipment used to mix acid and bicarbonate powders into concentrate at the user's facility.

Concentrates prepared from prepackaged salts and water at a dialysis facility for use in that facility are excluded from the scope of this International Standard. Although references to dialysis fluid appear herein, this International Standard does not address dialysis fluid as made by the end user. Also excluded from the scope of this International Standard are requirements for the monitoring frequency of water purity used for the making of dialysis fluid by the dialysis facility. Recommendations from the technical committee responsible for this International Standard for monitoring water quality are contained in ISO 23500. This International Standard does not address bags of sterile dialysis fluid or sorbent dialysis fluid regeneration systems that regenerate and recirculate small volumes of the dialysis fluid.

2 Normative references

The following documents, in whole or in part, are normatively referenced in this document and are indispensable for its application. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 11663, *Quality of dialysis fluid for haemodialysis and related therapies*

ISO 13959, *Water for haemodialysis and related therapies*

ISO 14971, *Medical devices — Application of risk management to medical devices*

IEC 60601-1, *Medical electrical equipment — Part 1: General requirements for basic safety and essential performance*

IEC 61010-1, *Safety requirements for electrical equipment for measurement, control, and laboratory use — Part 1: General requirements*

3 Terms and definitions

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

3.1
acetate concentrate
concentrated solution of salts containing acetate, which, when diluted with dialysis water, yields bicarbonate-free dialysis fluid for use in dialysis

Note 1 to entry: Acetate concentrate may contain glucose.

Note 2 to entry: Sodium acetate is used to provide a buffer in place of sodium bicarbonate.

Note 3 to entry: Acetate concentrate is used as a single concentrate.

3.2
acid concentrate
A-concentrate
acidified concentrated mixture of salts that, when diluted with dialysis water and bicarbonate concentrate, yields dialysis fluid for use in dialysis

Note 1 to entry: The term "acid" refers to the small amount of acid (for example, acetic acid or citric acid) that is included in the concentrate.

Note 2 to entry: Acid concentrate may contain glucose.

Note 3 to entry: Acid concentrate may be in the form of a liquid, a dry powder, other highly concentrated media, or some combination of these forms.

3.3
action level
concentration of a contaminant at which steps should be taken to interrupt the trend toward higher, unacceptable levels

3.4
additive
spike
small amount of a single chemical that, when added to the concentrate, will increase the concentration of a single existing chemical by a value labelled on the additive packaging

3.5
batch system
apparatus in which the dialysis fluid is prepared in bulk before each dialysis session

3.6
bicarbonate concentrate
B-concentrate
concentrated preparation of sodium bicarbonate that, when diluted with dialysis water and acid concentrate, makes dialysis fluid used for dialysis

Note 1 to entry: Sodium bicarbonate is also known as sodium hydrogen carbonate.

Note 2 to entry: Some bicarbonate concentrates also contain sodium chloride.

Note 3 to entry: Bicarbonate concentrate may be in the form of a liquid or a dry powder.

Note 4 to entry: Dry sodium bicarbonate, without added sodium chloride, is also used in concentrate generators to produce a concentrated solution of sodium bicarbonate used by the dialysis machine to make dialysis fluid.

3.7
bicarbonate dialysis fluid
dialysis fluid containing physiological or higher concentrations of bicarbonate

Note 1 to entry: Bicarbonate dialysis fluid is generally produced from two concentrates: one containing bicarbonate and the other containing acid and other electrolytes. See *acid concentrate* (3.2) and *bicarbonate concentrate* (3.6).

3.8
biofilm
microbially derived sessile community characterized by cells that are irreversibly attached to a substratum or interface or to each other, are imbedded in a matrix of extracellular polymeric substances that they have produced, and exhibit an altered phenotype with respect to growth rate and gene transcription

Note 1 to entry: The matrix, a slimy material secreted by the cells, protects the bacteria from antibiotics and chemical disinfectants.

Note 2 to entry: A certain amount of biofilm formation is considered unavoidable in dialysis water systems. When the level of biofilm is such that the action levels for microorganisms and endotoxins in the dialysis water cannot be routinely achieved, the operation of the system is compromised from a medical and technical point of view. This level of biofilm formation is often referred to as biofouling.

3.9
bulk delivery
delivery of large containers of concentrate to a dialysis facility

Note 1 to entry: Bulk delivery includes containers such as drums, which can be pumped into a storage tank maintained at the user's facility. Alternatively, the drums can be left at the facility and used to fill transfer containers to transfer the concentrate to the dialysis machines. Bulk delivery can also include large containers for direct connection to a central concentrate supply system.

Note 2 to entry: Bulk delivery also includes dry powder concentrates intended to be used with an appropriate concentrate mixer.

3.10
central concentrate system
system that prepares and/or stores concentrate at a central point for subsequent distribution to its points of use

3.11
central dialysis fluid delivery system
system that produces dialysis fluid from dialysis water and concentrate or powder at a central point and distributes the dialysis fluid from the central point to individual dialysis machines

3.12
concentrate generator
system where the concentrate is delivered to the user as a powder in a container, suitable for attachment to the dialysis machine with which it is intended to be used, and then the powder is converted into a concentrated solution by the dialysis machine

Note 1 to entry: The solution produced by the concentrate generator is used by the dialysis machine to make the final dialysis fluid delivered to the dialyser.

3.13
concentrate mixer
mixer for preparation of dialysis concentrate or dialysis fluid at a dialysis facility

3.14
device
individual water purification unit, such as a softener, carbon bed, reverse osmosis unit, or deionizer

Note 1 to entry: This term is synonymous with the term "component" as used by the US Food and Drug Administration (see Reference[15]).

3.15
dialysis fluid
dialysate
dialysis solution
aqueous fluid containing electrolytes and, usually, buffer and glucose, which is intended to exchange solutes with blood during haemodialysis

Note 1 to entry: The term "dialysis fluid" is used throughout this International Standard to mean the fluid made from dialysis water and concentrates that is delivered to the dialyser by the dialysis fluid delivery system. Such phrases as "dialysate" or "dialysis solution" are used in place of dialysis fluid in some countries; however, that usage is discouraged to avoid confusion.

Note 2 to entry: The dialysis fluid entering the dialyser is referred to as "fresh dialysis fluid", while the fluid leaving the dialyser is referred to as "spent dialysis fluid."

Note 3 to entry: Dialysis fluid does not include prepackaged parenteral fluids used in some renal replacement therapies, such as haemodiafiltration and haemofiltration.

3.16
dialysis fluid delivery system
device that: prepares dialysis fluid online from dialysis water and concentrates or that stores and distributes premixed dialysis fluid; circulates the dialysis fluid through the dialyser; monitors the dialysis fluid for temperature, conductivity (or equivalent), pressure, flow and blood leaks; and, prevents dialysis during disinfection or cleaning modes

Note 1 to entry: The term includes reservoirs, conduits, proportioning devices for the dialysis fluid, and monitors and associated alarms and controls assembled as a system for the purposes listed above.

Note 2 to entry: The dialysis fluid delivery system can be an integral part of a single-patient dialysis machine or a centralized preparation system which feeds multiple bedside monitoring systems.

Note 3 to entry: Dialysis fluid delivery systems are also known as proportioning systems and dialysis fluid supply systems.

3.17
dialysis water
water that has been treated to meet the requirements of ISO 13959 and which is suitable for use in haemodialysis applications, including the preparation of dialysis fluid, reprocessing of dialysers, preparation of concentrates, and preparation of substitution fluid for online convective therapies

3.18
disinfection
destruction of pathogenic and other kinds of microorganisms by thermal or chemical means

Note 1 to entry: Disinfection is a less lethal process than sterilization because it destroys most recognized pathogenic microorganisms but does not necessarily destroy all microbial forms.

3.19
endotoxin
major component of the outer cell wall of gram-negative bacteria

Note 1 to entry: Endotoxins are lipopolysaccharides, which consist of a polysaccharide chain covalently bound to lipid A. Endotoxins can acutely activate both humoral and cellular host defences, 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. [See also *pyrogen* (3.30).]

3.20
endotoxin units
EU
units assayed by the *Limulus* amoebocyte lysate (LAL) test when testing for endotoxins

Note 1 to entry: Because activity of endotoxins depends on the bacteria from which they are derived, their activity is referred to a standard endotoxin.

Note 2 to entry: In some countries, endotoxin concentrations are expressed in international units (IU). Since the harmonization of endotoxin assays, EU and IU are equivalent.

3.21
germicide
agent that kills microorganisms

3.22
haemodiafiltration
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

Note 1 to entry: Diffusive solute removal is achieved using a dialysis fluid stream as in haemodialysis. 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 replacement solution into the blood either before the dialyser (predilution haemodiafiltration) after the dialyser (postdilution haemodiafiltration), or a combination of the two (mixed dilution haemodiafiltration).

3.23
haemodialysis
form of renal replacement therapy in which waste solutes are removed primarily by diffusion from blood flowing on one side of a membrane into dialysis fluid flowing on the other side

Note 1 to entry: Fluid removal that is sufficient to obtain the desired weight loss is achieved by establishing a hydrostatic pressure gradient across the membrane. This fluid removal provides some additional waste solute removal, particularly for solutes with higher molecular weight.

3.24
haemofiltration
form of renal replacement therapy in which waste solutes are removed from blood by convection

Note 1 to entry: Convective transport is achieved by ultrafiltration through a high-flux membrane. Fluid balance is maintained by infusing a replacement solution into the blood either before the haemofilter (predilution haemofiltration), after the haemofilter (postdilution haemofiltration) or a combination of the two (mixed dilution haemofiltration).

Note 2 to entry: There is no dialysis fluid stream in haemofiltration.

3.25
***Limulus* amebocyte lysate test**
LAL test
assay used to detect endotoxin

Note 1 to entry: The detection method uses the chemical response of an extract from blood cells of a horseshoe crab (*Limulus polyphemus*) to endotoxins.

Note 2 to entry: Amebocyte lysate from a second horseshoe crab, *Tachypleus tridentatus*, may also be used to detect endotoxin.

3.26
manufacturer
entity that designs, manufactures, fabricates, assembles, or processes a finished device

Note 1 to entry: Manufacturers include, but are not limited to, those who perform the functions of contract sterilization, installation, relabelling, remanufacturing, repacking, or specification development, and initial distributions of foreign entities performing these functions. The term does not cover preparation of concentrates from prepackaged dry chemicals at a dialysis facility or the handling of bulk concentrates at a dialysis facility after responsibility for the concentrate is transferred from the manufacturer to the user.

3.27
microbiological contamination
contamination with any form of microorganism (e.g. bacteria, yeast, fungi, and algae) or with the by-products of living or dead organisms such as endotoxins, exotoxins, and cyanobacterial toxins (derived from blue-green algae)

3.28
nonpyrogenic
not eliciting a pyrogen reaction

Note 1 to entry: Historically, the threshold pyrogenic dose of 5 EU/kg/h (the minimum dose that produces fever) has been used to set endotoxin limits of devices and injectable medications.

Note 2 to entry: The volume of fluid administered should not exceed the volume that would result in a total dose of endotoxin of ≥5 EU/kg/h.

Note 3 to entry: This definition is applicable for fluids produced by online techniques, e.g. substitution and priming fluids.

Note 4 to entry: The commonly used gel clot method has a sensitivity limit of 0,03 EU/ml.

3.29
proportioning system
apparatus that proportions dialysis water and haemodialysis concentrate to prepare dialysis fluid

3.30
pyrogen
fever-producing substance

Note 1 to entry: Pyrogens are most often lipopolysaccharides of gram-negative bacterial origin [see also *endotoxin* (3.19)].

3.31
sodium hypochorite
chemical used for disinfection of haemodialysis systems

Note 1 to entry: Commercially available solutions of sodium hypochlorite are known in different countries by terms such as bleach and javel. These solutions are used for disinfection at concentrations recommended by equipment manufacturers.

3.32
sterile
free from viable microorganisms

Note 1 to entry: “Sterile” can be used to describe a packaged solution that was prepared using a terminal sterilization process validated according to the methods of the applicable pharmacopoeia. A terminal sterilization process is commonly defined as one that achieves a sterility assurance level (SAL) of 10^{-6}, i.e. assurance of less than one chance in a million that viable microorganisms are present in the sterilized article.

Note 2 to entry: Alternatively, “sterile” can be used to describe a solution prepared for immediate use by a continuous process, such as filtration, that has been validated according to the methods of the applicable pharmacopoeia to produce a solution free from microorganisms for the validated life of the filter.

3.33
storage tank
tank at the user’s facility for storage of dialysis water or concentrate from bulk deliveries, or for concentrate prepared in bulk at the user’s facility from powder and dialysis water

3.34
substitution fluid
fluid used in haemofiltration and haemodiafiltration treatments which is infused directly into the patient's blood as a replacement for the fluid that is removed from the blood by filtration

Note 1 to entry: Substitution fluid is also referred to as substitution solution or replacement solution.

Note 2 to entry: Substitution fluid may also be used for bolus administration, for priming of an extracorporeal blood circuit, and for returning blood to the patient at the end of a treatment.

3.35
user
physician or physician's representative or healthcare professional with a responsibility for the prescription, production, and delivery of dialysis fluid

4 Requirements

4.1 Concentrates

4.1.1 Physical state

The concentrate for haemodialysis may be supplied in dry or aqueous form. Packaging may be for direct use with a single dialysis machine or for use in systems supplying multiple dialysis machines (bulk use).

4.1.2 Solute concentrations

4.1.2.1 Liquid solute concentrations

All electrolytes identified on the label shall be present within ±5 % or ±0,1 mEq/l (expressed as dialysis fluid concentrations), whichever is greater, of the stated concentration, with the exception of sodium, which shall be present within ±2,5 % of the labelled concentration, or shall be present according to approved specifications by the local regulations. If used, glucose shall be present within ±5 % or ±0,05 g/l (when measured as properly diluted dialysis fluid), whichever is greater, of the labelled concentration, or shall be present according to approved specifications by the local regulations. Where concentrates include non-traditional constituents, such as antioxidants and iron compounds, these constituents shall be present at nominal concentrations with ±5 % tolerances, or shall be present according to approved specifications by the local regulations. If alternate, locally approved tolerances are used, the tolerances shall be similarly stated and the rationale for their use documented.

Most concentrates are manufactured with standard traditional chemicals such as sodium chloride, potassium chloride, magnesium chloride, calcium chloride, acetic acid, glucose, etc. New concentrates are available in which certain chemicals have been substituted by others; for example, citric acid has been substituted for acetic acid. Where this occurs, the labelling shall correctly reflect this and the substitute chemicals shall be present at nominal concentrations with ±5 % tolerances, or shall be present according to approved specifications by the local regulations. If alternate, locally approved tolerances are used, the tolerances shall be similarly stated and the rationale for their use documented.

4.1.2.2 Solute concentrations from powder

When concentrate is packaged in dry form or a combination of dry and liquid and is mixed according to the manufacturer's instruction for use, the final concentrate shall meet the requirements of 4.1.2.1.

4.1.3 Water

The quality of water used in the manufacture of the concentrate shall be in accordance with ISO 13959.

4.1.4 Bacteriology of concentrates

4.1.4.1 Bacteriology of bicarbonate concentrates

Concentrate containing bicarbonate supplied as a liquid shall be provided in a sealed container and manufactured by a process validated to produce dialysis fluid meeting the microbiological requirements of ISO 11663, when used according to the manufacturer's instructions. Bicarbonate powder intended for the preparation of concentrate at a dialysis facility shall be capable of producing dialysis fluid meeting the microbiological requirements of ISO 11663, when used according to the manufacturer's instructions.

4.1.4.2 Bacteriology of acid concentrates

There are no published reports of acid concentrate supporting bacterial growth and as such, acid concentrate need not be tested for bacterial growth.

4.1.5 Endotoxin levels

The concentrate shall be formulated and packaged using a process validated to produce dialysis fluid meeting the endotoxin requirements of ISO 11663 or the applicable pharmacopoeia when used according to the manufacturer's instructions.

4.1.6 Fill quantity

The excess fill volume of liquid containers and the excess fill weight of powder containers used with batch systems for a single dialysis treatment shall be within 2 % of the labelled volume or weight. The fill weight of bulk delivered powdered concentrate shall be such that, when mixed according to the manufacturer's instructions, it produces liquid concentrate that meets the requirements of 4.1.2.1. The fill weight of a concentrate generator shall be such that the device performs as intended. For all other applications, the fill volume or weight shall be ≥100 % of the stated volume or weight.

4.1.7 Chemical grade

All chemicals shall meet the requirements of the applicable pharmacopoeia, 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, any pharmacopoeia requirements that the chemicals be labelled for use in haemodialysis need not be complied with if the manufacturer is performing its own testing to meet the requirements of the applicable pharmacopoeia.

4.1.8 Particulates

The aqueous dialysis concentrate shall be filtered through a nominal 1 µm or finer particulate filter. The particulate filter used shall have a non-fibre-releasing membrane that does not contain material of known potential for human injury.

4.1.9 Additives — "Spikes"

If additives are supplied, the concentration, when properly diluted with water or concentrate, shall yield values within ±5 % by weight of the labelled value.

4.1.10 Containers

Containers, including the closures, shall not interact chemically or physically with the contents 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 to indicate its contents. One means of indicating the contents is to use an appropriate symbol (see Table 2).

4.1.11 Bulk-delivered concentrate

When concentrate is delivered in bulk form, the responsibility for ensuring compliance with this International Standard shall pass from the manufacturer to the user at 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 with appropriate labels and non-tamper procedures.

4.1.12 Concentrate generators

Concentrate generator systems include systems that mix powder, or powder and a highly concentrated liquid, into a concentrate by forming a slurry or concentrated solution in a container designed to function with specific dialysis machines. Mixing is accomplished by an automated dynamic proportioning system within the dialysis fluid delivery system. Because these concentrates are delivered to the user as a powder or a highly concentrated liquid in containers designed for specific machines, it is the concentrate generator manufacturer's responsibility to ensure that

— all applicable clauses of this document dealing with powder are met,

— the container will function with the machines as defined by the manufacturers of the machines, and

— undissolved powder is prevented from entering the dialysis fluid stream.

4.2 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 product so as to significantly alter the strength, purity, or quality of the concentrate delivered to the user. Examples of materials that should not be used in manufacturing equipment include copper, brass, zinc, galvanized material, or aluminium.

4.3 Systems for mixing concentrate at a dialysis facility

4.3.1 General

The following requirements apply to systems, such as a central concentrate system, used to prepare acid or bicarbonate concentrates from dialysis water and powder or other highly concentrated media at a dialysis facility.

4.3.2 Materials compatibility

The materials of any components of concentrate mixing devices/systems (including storage and distribution systems) that contact the concentrate solutions shall not interact chemically or physically so as to adversely affect their purity or quality. Such components shall be fabricated from non-reactive materials (e.g. plastics) or appropriate stainless steel. The use of materials that are known to cause toxicity in haemodialysis, such as copper, brass, zinc, galvanized material, or aluminium, are specifically prohibited.

4.3.3 Disinfection protection

4.3.3.1 General

When the manufacturer of the mixing system recommends chemical disinfectants [see 6.7.2 k)], means shall be provided to restore the system to a safe condition relative to residual disinfectant prior to the system being used to prepare a batch of concentrate. When formaldehyde is used, the residual level shall be less than 3 mg/l; when sodium hypochlorite is used, the residual level shall be less than 0,1 mg/l; when ozone is used, the residual level shall be less than 0,1 mg/l; when a commercially available chemical germicide other than formaldehyde, sodium hypochlorite, or ozone is used, the residual level shall

be less than that recommended by the manufacturer of the specific germicide. When recommending chemical disinfectants, the manufacturer shall also recommend methods for testing for residual levels of the disinfectants.

When the manufacturer of the mixing system recommends high-temperature disinfection, a means shall be provided to restore the system to a safe temperature prior to being used to prepare a batch of concentrate.

4.3.3.2 System lock out

When disinfection is accomplished automatically by chemical disinfectant, ozone, or by high temperature procedures, activation of the disinfection system shall result in activation of a warning system and measures should be taken to isolate haemodialysis machines from the concentrate preparation and distribution system.

4.3.4 Safety requirements

Each concentrate mixing device/system shall exhibit the following minimum safety features:

a) operating controls shall be positioned so as to minimize inadvertent operation and resetting of functions;

b) distribution controls shall be clearly labelled to minimize the possibility of error in the transfer of concentrate.

4.3.5 Bulk storage tanks

When used for bicarbonate concentrate, storage tanks should have a conical or bowl-shaped base and should drain from the lowest point of the base. Bicarbonate storage tanks should have a tight fitting lid to prevent ingress of contaminants and be vented through a hydrophobic 0,45 µm air filter.

Rigid, non-flexing acid concentrate storage tanks may have a flat bottom and should be vented in a way to prevent dirt contamination of the concentrate.

Storage tanks should not have sight tubes, which can grow algae and fungi. Means shall be provided to effectively disinfect any storage tank in a concentrate distribution system that is subject to microbiological contamination.

The disinfection of acid concentrate tanks is normally not necessary. However, bicarbonate tanks should be disinfected frequently. For acid concentrate storage alternative bulk storage containers, such as bladders, may be used.

4.3.6 Ultraviolet irradiators

When concentrate storage and distribution systems are provided with an ultraviolet irradiator for bacterial control, the following shall be complied with:

a) the ultraviolet irradiator shall emit radiation at a wave frequency of 254 nm;

b) the ultraviolet irradiator shall provide a dose of radiant energy of 16 mW·s/cm^2 if it is fitted with a calibrated ultraviolet intensity meter, otherwise it shall provide a dose of radiant energy of 30 mW s/cm^2;

c) the ultraviolet irradiator shall be sized appropriately for the maximum flow rate;

d) the ultraviolet irradiator shall be equipped with an online monitor of radiant energy output or a recommended frequency of lamp replacement shall be stated;

e) the ultraviolet irradiator shall be followed by an endotoxin-retentive filter.

4.3.7 Piping systems

Concentrate distribution systems shall not contribute microbiological contaminants to the concentrate. Concentrate distribution systems shall be designed and operated in a manner that minimizes bacterial proliferation and biofilm formation that can contaminate susceptible concentrates. Frequent disinfection of bicarbonate concentrate distribution systems is one way to minimize bacterial proliferation and biofilm. The disinfection of piping systems for acid concentrate is normally not necessary because acid concentrates are typically bacteriostatic.

4.3.8 Electrical safety requirements

Where there is a possibility of a sustainable fluid pathway to the patient which is capable of conducting electrical current, the device shall meet the requirements of IEC 60601-1 with respect to electrical safety. Where the electrical system is isolated from the patient the device shall meet the requirements of IEC 61010-1, with respect to electrical safety.

NOTE There is a possibility of a sustainable fluid pathway to the patient which is capable of conducting electrical current. Its existence would depend on the distribution system and the manufacturer's instructions for use of the concentrate mixing system. To maximize electrical safety two cases are presented: a) where there is a possibility of a sustainable electrical pathway and b) where the electrical system is isolated from the patient.

5 Tests

5.1 General

Clause 5 defines test methods by which compliance with the requirements of Clause 4 can be verified. 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 provided such methods have been appropriately validated, and compared to the cited methods.

5.2 Concentrates

5.2.1 Physical state

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

5.2.2 Solute concentrations

5.2.2.1 Liquid solute concentrations

Compliance with the requirements of 4.1.2.1 for calcium, potassium, magnesium and sodium can be determined by using methods described by the American Public Health Association,[7] methods referenced by the US. Environmental Protection Agency,[12] methods referenced in applicable pharmacopoeia, or other equivalent validated analytical methods. Samples shall be collected in sealed containers. Appropriate sample preparation, including using suitable mixing vessels and adjusting for pH if necessary, shall be used to ensure accurate determinations.

Compliance with the requirements of 4.1.2.1 for new and non-traditional concentrate constituents can be determined by using appropriate and validated analytical methods.

The maximum contaminant levels referred to in ISO 13959 shall be used as a reference for dialysis water.

Compliance with the requirements for the contents of the dialysis fluid can be determined as described in Table 1.Other test methods may also be used, provided such methods have been appropriately validated, and compared to the cited methods.

Table 1 — Analytical tests for chemical components

Component	Test methods
Acetate	Gas chromatography, liquid chromatography, enzymatic, or potentiometric methods
Bicarbonate	Acid titration and calculation, ion chromatography, or other method for total CO_2
Calcium	EDTA titrimetric method, or atomic absorption (direct aspiration), inductively coupled plasma spectrometry (direct aspiration) or ion chromatography
Glucose	Polarimetry, enzymatic, liquid chromatography, or chemical methods
Magnesium	Atomic absorption (direct aspiration), inductively coupled plasma spectrometry (direct aspiration), or ion chromatography
Potassium	Flame photometry method, atomic absorption (direct aspiration), inductively coupled plasma spectrometry (direct aspiration) or ion chromatography
Sodium	Atomic absorption (direct aspiration), flame photometric method, inductively coupled plasma spectrometry (direct aspiration), ion-specific electrode, or ion chromatography

5.2.2.2 Solute concentrations from powder

To test for the solute concentration from dry powders the contents of a package should be mixed according to the manufacturer's instructions and tested according to 5.2.2.1.

5.2.3 Water

Compliance with the water quality requirements of 4.1.3 can be determined by using methods referenced in this International Standard.

5.2.4 Bacteriology of bicarbonate concentrates

To ensure compliance with 4.1.4 the following procedure can be used. Total viable counts (standard plate counts) shall be obtained using the membrane filter technique or other validated standard bacteriology test methods. The calibrated loop technique shall not be used. Culture media shall be tryptone glucose extract agar (TGEA) or Reasoner's 2A supplemented with 4 % sodium bicarbonate, or equivalent.

Blood or chocolate agar shall not be used. Incubation temperatures of 17 °C to 23 °C, and an incubation time of 168 h (7 d) are recommended. Other test methods may also be used, provided such methods have been appropriately validated, and compared to the cited methods.

5.2.5 Endotoxin levels

Compliance with the requirements of 4.1.5 can be determined by the LAL test for endotoxins.

5.2.6 Fill quantity

Compliance with the requirements of 4.1.6 can be determined by the use of appropriate volumetric or gravimetric techniques.

5.2.7 Chemical grade

Purity of chemicals as specified in 4.1.7 can be determined by test methods outlined in the appropriate pharmacopoeia.

5.2.8 Particulates

Compliance with the requirements of 4.1.8 can be determined by inspection of the manufacturing records of the product to ensure that the concentrate was filtered through a nominal 1 µm filter.

5.2.9 Additives — "Spikes"

Compliance with 4.1.9 may be determined by dissolving the additive in the appropriate concentrate and then measuring the concentration of the added chemical to determine if the presence of the additive altered the concentration of that chemical to within ±5 % of the amount specified on the additive label. Alternately, the additive may be diluted into the appropriate quantity of water and tested to determine if the additive provides the stated increase in concentration within ±5 % of the labelled value. Testing should be done according to 5.2.2.1 once the additive is mixed.

5.2.10 Containers

Compliance with the requirements of 4.1.10 can be determined by visual inspection and by appropriate biocompatibility testing. Biocompatibility testing should begin with a risk analysis. Using the results of that risk analysis a testing rationale should be developed using, for example, methods described in applicable pharmacopoeia or other appropriate documents.

5.2.11 Bulk delivered concentrate

Compliance with the requirements of 4.1.11 can be determined by review of the delivery procedures.

5.2.12 Concentrate generators

Compliance with 4.1.12 can be confirmed by review of the design records of the container that holds the powder, functional testing with the intended haemodialysis machine and inspection of the product label.

NOTE It is recognized that a dialysis machine manufacturer could modify his equipment to use another manufacturer's concentrate generator system. When this occurs it becomes the machine manufacturer's responsibility to ensure that the concentrate generator system is compatible with the dialysis machine.

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 non-reactive materials (e.g. plastics or appropriate stainless steel) that are not known to cause toxicity in dialysis fluid systems. Biocompatibility testing should begin with a risk analysis. Using the results of that risk analysis a testing rationale should be developed using, for example, methods described in applicable pharmacopoeia or other appropriate documents.

5.4 Systems for mixing concentrate at a dialysis facility

5.4.1 General

The following test methods apply to 4.3.2 to 4.3.8, as indicated.

5.4.2 Materials compatibility

Compliance with the requirements of 4.3.2 can be verified by visual inspection and by appropriate biocompatibility testing. Biocompatibility testing should begin with a risk analysis. Using the results of that risk analysis a testing rationale should be developed using, for example, methods described in applicable pharmacopoeia or other appropriate documents.

5.4.3 Disinfection protection

5.4.3.1 General

Compliance with the requirements of 4.3.3.1 can be determined by testing for the disinfectant in the rinse water at the end of the disinfection loop. When the disinfectant is formaldehyde, residual levels can be determined by the Hantzsch reaction, Schiff's reagent or an equivalent test. When the disinfectant is sodium hypochlorite, residual levels can be determined using the DPD ferrous titrimetric methods or an equivalent test. When the disinfectant is ozone, residual levels can be determined using an online monitor for dissolved ozone or analysis of water samples using test kits based on indigo trisulfonate or DPD chemistry. If a commercially available chemical germicide other than formaldehyde, sodium hypochlorite, or ozone is used, the test established by the manufacturer of the germicide for residual germicide shall be used according to the test manufacturer's instructions.

Compliance with the requirements of 4.3.3.1 for high-temperature disinfection can be shown by demonstrating that the rinse water has returned to a safe temperature.

5.4.3.2 System lock out

Compliance with the requirements of 4.3.3.2 can be determined by physical test and/or visual inspection.

5.4.4 Safety requirements

Compliance with 4.3.4 can be determined by inspection.

5.4.5 Bulk storage tanks

Compliance with the requirements of 4.3.5 can be determined by visual inspection.

5.4.6 Ultraviolet irradiators

Compliance with 4.3.6 can be determined by inspection.

5.4.7 Piping systems

The absence of aluminium, copper, lead, zinc, and galvanized components and the configuration of a concentrate mixing system/device can be determined by visual inspection. Non-contribution of bacteria and specific chemical contaminants to the solution by the distribution system can be verified by using the tests described in 5.2.4 and 5.3.

5.4.8 Electrical safety requirements

Compliance with the requirements of 4.3.8 can be determined using the tests found in IEC 60601-1 or IEC 61010-1 as appropriate.

6 Labelling

6.1 General

The term "labelling" in this International Standard includes any written material accompanying the haemodialysis concentrates and concentrate mixing system or any written instructions provided by the manufacturer.

The label on the concentrate container shall, at a minimum, provide the applicable information contained in 6.2 to 6.6. Symbols may be used where appropriate.

NOTE 1 See ISO 15223.

NOTE 2 With some machines the mixing of concentrate is automated and not performed by the user. In these cases the instructions for use can be modified to fit the appropriate situation. For example, if the machine takes powder and liquid concentrate and mixes them internally, it would not be necessary to state that the "concentrate be mixed well before use." The design of the machine should take this into account and mix the concentrate appropriately.

6.2 General labelling requirements for concentrates

General labelling requirements for concentrates shall include the following.

a) Name and address of the manufacturer/distributor.

b) Expiry date, if applicable.

NOTE Normally, the expiry date and not the manufacturing date will be on the product.

c) Manufacturing date, only if expiry date is not applicable.

d) Identifying lot number.

e) A list of all ingredients in the final concentrate and the following.

f) Composition, including the concentration, in grams per litre (g/l), of each ingredient for liquid concentrate or the weight per container of each ingredient for powder.

g) Composition of the dialysis fluid, including the nominal concentration of each electrolyte in millequivalents per litre (mEq/l) or millimoles per litre (mmol/l) and the concentration of non-electrolytes in the dialysis fluid in grams per litre (g/l) or mmol/l; the chemical concentration of the final dialysis fluid shall be placed on the acid concentrate label.

NOTE Where there is insufficient space on the label to properly present the information required, it is acceptable to provide this information in an alternative format such as a package insert.

h) For batch systems, the volumes or weight of dialysis concentrate(s) and the amount and quality of the water that shall be mixed; if mixing is automated an instruction to follow the manufacturer's instructions for use.

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

j) Trade name of the product, if appropriate.

k) A statement regarding storage requirements such as, if appropriate: "Store at or below room temperature"; "Do not freeze"; and/or "Short-term exposure to warm conditions (40 °C) will not harm acid concentrate".

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

m) A warning stating that bacterial growth can occur when using bicarbonate concentrate (bicarbonate concentrate only) and any other precautions that shall be taken in the mixing of the concentrate.

n) When appropriate, a statement to test the final dialysis fluid for one of the following parameters: conductivity, pH, osmotic pressure, sodium concentration, or chloride concentration.

o) A statement that ISO-quality water meeting the requirements of ISO 13959 shall be used to dilute the concentrate to make dialysis fluid.

p) A statement to not overmix bicarbonate concentrate.

q) A statement regarding any special buffering concerns (including the impact of varying the dialysis fluid sodium and bicarbonate concentration during dialysis) on the labelled composition of the final dialysis fluid, if appropriate (see A.2.1.1)".

6.3 Labelling requirements for liquid concentrate

Labelling for liquid concentrate shall include the following.

a) Instructions for use.

   1) The label shall include instructions to mix thoroughly prior to use and instructions not to use damaged containers. When bicarbonate is used, a warning shall be included noting that bacterial growth can occur in concentrated or diluted bicarbonate solutions.

   2) The labelling shall state that once opened, the bicarbonate concentrate shall be used within the time limit specified by the manufacturer, or within 24 h, 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 dialysis fluid that meets the chemical and microbiological recommendations of ISO 11663 when used in a properly maintained system.

   3) Liquid concentrate labelling may include geometric symbols (see Table 2) to differentiate different proportioning ratios. If such symbols are used, the numbers representing the proportioning system should also be easily visible and located within the boundaries of the geometric symbol. The label should incorporate a means to differentiate between acid and bicarbonate. If a concentrate contains no potassium or no calcium, that shall be prominently displayed on the label. If colour coding is used, red should be used for acid, blue for bicarbonate, and white for acetate.

b) Fill volume of the container.

c) Nominal conductivity of the final dialysis fluid when mixed according to the manufacturer's instructions or a statement that such information is available from the manufacturer.

6.4 Labelling requirements for powder concentrate

Labelling for powder concentrate shall include the following.

a) Instructions for use.

   1) 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 stated. The maximum storage time (shelf life) before dissolution and following dissolution shall be stated for specified storage conditions. 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 (e.g. conductivity or pH) to ensure proper dilution of the final dialysis fluid, and any specific precautions that shall be followed to ensure proper use of the product.

   2) Powder concentrate labelling may include geometric symbols (see Table 2) to differentiate different proportioning ratios. If such symbols are used, the numbers representing the proportioning system should also be easily visible and located within the boundaries of the geometric symbol. The label should incorporate a means of differentiating between acid and bicarbonate. If a concentrate contains no potassium or no calcium, that shall be prominently displayed on the label. If colour coding is used, red should be used for acid and blue for bicarbonate.

b) Instructions for mixing the dry powders into a liquid concentrate.

c) The amount of water that shall be used to reconstitute the concentrate.

d) If applicable, the mixing equipment for which the powder is to be used.

e) 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.

f) The water quality that should be used to mix the concentrate (i.e. the maximum bacterial and endotoxin levels).

6.5 Additives

Labelling for additives shall include the following.

a) A list of the product(s) for which the additive can be used. The effective changes in the concentrate formula and the subsequent change to the dialysis fluid, which result from the addition of the additive.

b) Dilutional effects on the final dialysis fluid of any liquid additives (labelling on liquid additives only).

6.6 Labelling requirements for concentrate generators

Labelling for concentrate generators shall include the following.

a) Proportioning system or dialysis machine with which they are to be used.

NOTE It is possible that a manufacturer could modify his machine to accept another manufacturer's concentrate generator system. In this case the machine manufacturer has the responsibility to label the machine with the correct concentrate generator system model and manufacturer.

b) The amount of time that the concentrate generator can reasonably be expected to provide solution, based on a manufacturer's specified flow rate to the dialyser (e.g. 6 h at a flow rate of 500 ml/min.); alternatively, the capacity of the concentrate generator can be expressed as the volume of concentrate which can be produced by the concentrate generator.

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

Table 2 — Symbols for concentrate container system: concentrate types

Designation					**Other**[a] (new)
Mix ratio[bc]	1:1,23:32,77	1:1,83:34	1:1.72:42,28	1:1,1:34	TBD[a]
Acid mix ratio[de]	1:34	1:35,83	1:44	1:35,1	TBD[a]
Bicarbonate mix ratio[fg]	1:27,46	1:19,13	1:25,16	1:31,8	TBD[a]
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 (to be determined).

[b] Acid:bicarbonate:water.

[c] There can be minor differences in mix ratios within each concentrate type; e.g. 1:1,18:32,82 and 1:1,26:32,74 can be used instead of 1:1,23:32,77, and 1:1,58:42,42 can be used instead of 1:1,72:42,28.

[d] Acid:water + bicarbonate concentrate.

[e] The acid mix ratio may also be expressed as acid + (water + bicarbonate concentrate); e.g. 1 + 34, and 1 + 44, can be used instead of 1:34 and 1:44, respectively.

[f] Bicarbonate: acid + water.

[g] Bicarbonate mix ratios are based on 8,4 % sodium bicarbonate solution (1 000 mmol/l). Other solutions may be used clinically and their use will result in a different mixing ratio.

6.7 Labelling for concentrate mixer systems

6.7.1 General

Labelling for concentrate mixing devices shall include the following:

a) name and address of manufacturer (affixed to the device);

b) trade name and type of device (affixed to the device);

c) model and serial number (affixed to the device);

d) warning that product literature should be read before use of the concentrate mixing system;

e) prominent warnings about substances (e.g. germicides) that need to be removed from the device before using the device;

f) identification of fitting type or specification when necessary to prevent improper connections (preferably attached to the device, but otherwise included in the instructions for use).

6.7.2 Product literature for concentrate mixers

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

a) a warning that each batch of concentrate should be tested according to the manufacturer's instructions before use;

b) a warning that selection of concentrate mixing equipment for dialysis is the responsibility of the dialysis physician;

c) a description of the device or system, including a list of monitors, alarms, and component devices provided as standard equipment;

d) a schematic diagram of the device or system showing the location of any valves, online monitors, or sampling ports;

e) operating specifications, such as water pressure and flow rate;

f) 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;

g) safety features and warnings concerning the consequences if these features are circumvented;

h) information pertaining to online monitors of water or concentrate quality, including operational factors that could affect monitor performance (e.g. temperature);

i) construction materials, identified generically, that are in contact with solutions;

j) information about germicides and cleaning agents known to be compatible with materials used in the device, as well as information about known chemicals with which materials used in the construction of the device are incompatible;

k) if applicable, a method of cleaning and disinfecting the equipment, the time interval between cleanings and disinfections of the system, and a method of removing the residual germicide;

l) other maintenance and service instructions, including recommended preventive maintenance procedures, and schedules, recommended monitoring schedules, trouble-shooting guidelines intended for the user, service information, a recommended spare parts list, a warning of the consequences if maintenance instructions are not followed;

m) a warning that if, after installation and subsequent use, any component of the concentrate mixing system is changed or replaced, the user should conduct appropriate tests and calibrations;

n) where ultraviolet irradiators are used, the necessary maintenance steps, such as bulb replacement and cleaning, to maintain the system.

Annex A
(informative)

Rationale for the development and provisions of this International Standard

A.1 Scope

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

Systems that regenerate dialysis fluid by passing the dialysis fluid through systems to restore the dialysis fluid's original content have been specifically excluded from the scope of this International Standard.

Concentrate solutions for use in preparing dialysis fluid for haemodialysis, 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 could produce confusion as to the duties and liabilities of the parties involved.

The concentrate, properly manufactured and labelled, could be used in erroneous combinations; the correct option might not be used for a given patient; improper handling could lead to contamination of the final dialysis fluid. 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.

Clinical experience has made it clear that prescribing physicians might not be fully aware of the amounts of buffer that are added as the result of acetate (when present in liquid concentrate) and acetate and acetic acid (sodium hydrogen diacetate) (when present in dry concentrate). These add ≥6 mEq/l of anion, which is capable of being metabolised to generate bicarbonate. This being in addition to whatever bicarbonate concentration is prescribed and make the final buffer concentration unexpectedly high.

While the principal concern is for adequate, safe treatment of the patient, other considerations have influenced the content of this International Standard such as theoretical hazards, or remote short- or long-term risks. Haemodialysis is a complicated procedure. Therefore, an attempt has been made to set standards that are consistent with operating 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 burden 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.2 Requirements

A.2.1 General

A.2.1.1 Overview

The display of identification data and basic content information provides necessary information for use and reference and ensures traceability. The use of bicarbonate dialysis fluid requires two concentrates to be used in preparing dialysis fluid because concentrated calcium and bicarbonate will precipitate when 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 made into a concentrated solution by the dialysis fluid delivery system. 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 dialysis fluid 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 dialysis fluid is the responsibility of the end user. When calculating the total amount of base in the final dialysis fluid, the contribution of acetate (or any other organic anion that produces bicarbonate as it is metabolised) from the acid concentrate should be taken into account, since this contribution is additive to the bicarbonate contained in the bicarbonate concentrate.

Some acid concentrates, such as those formulated with sodium hydrogen diacetate (a compound comprised of acetic acid and sodium acetate), contain more organic anions than traditional concentrates. When using one of these concentrates, consideration should be given to the significant increase in base derived from the acid concentrate when selecting a dialysis fluid bicarbonate concentration.

Standards for bicarbonate dialysis fluid delivery systems thus should address both proportioning and monitoring systems, as well as concentrate packaging and labelling.

In view of the potential for improper use of concentrate, a decision has been made to emphasize the importance of user education and training and to specify labelling.

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

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

Acetate concentrate is a single component concentrate that uses sodium acetate as the buffer rather than bicarbonate. As technology has advanced, the use of acetate concentrate has diminished.

A.2.1.2 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.2.1.3 Solute concentrations

It is essential that the actual concentrations of the solutes contained in the concentrate be as close as possible to the labelled amount. Although excessive variations could be hazardous to the patient,

tolerances of less than 5 % for glucose and the minor cations can 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 glucose 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.

A.2.1.4 Water

It was 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. Accordingly, the requirements for water in ISO 13959 were referenced.

A.2.1.5 Bacteriology of bicarbonate concentrates

Bicarbonate concentrates have been shown to support bacterial growth and to provide another source of initial bioburden capable of rapid increase after dilution.[9][8] 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 shall be recommended by manufacturers and established and followed by users.

There has been considerable discussion regarding the use of appropriate media and incubation conditions to culture bicarbonate concentrate. This International Standard gives one acceptable method described in 5.2.4. Other methods may be used, provided that such methods have been appropriately validated and compared to the cited methods.

Most microorganisms do not grow well in acid concentrates and thus, there is no requirement for testing for release levels of bacteria in acid concentrate.

A.2.1.6 Fill quantity

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

A.2.1.7 Chemical grade

It is recommended that all chemicals meet the requirements of the applicable pharmacopoeia. The limits of sodium, potassium, calcium, magnesium, and pH may be exceeded, provided that the exceptions are compensated for in the final formula. 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 burden of meeting these limits.

It was also considered whether or not chemicals to be used in haemodialysis should be so labelled. Since the labelling requirement did not reflect any change in pharmacopoeia specifications, it was decided that such a requirement would not increase product quality.

A.2.1.8 Additives — “Spikes”

All substances in the final concentrate should 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 could diffuse into the bloodstream. Preservatives or indicators present in the concentrate should be indicated on the label.

A.2.1.9 Containers

Substances from the containers that contaminate the concentrate could diffuse into the patient during dialysis and could cause harm to the patient. Therefore, relatively non-reactive containers that would not affect strength or purity of the concentrate should be used.

A.2.1.10 Endotoxin levels

Control of endotoxin in the concentrate is necessary to prevent pyrogenic reactions in the patient during dialysis. An endotoxin limit was deemed to be appropriate for the water and dialysis fluid because evidence was presented that it was possible for pyrogens in the dialysis fluid to enter the patient. This limit was set in ISO 11663 because the final dialysis fluid has the greatest effect on the patient and the dialysis fluid is a combination of many factors such as the bacterial status of the concentrate, water, and the cleanliness of the dialysis machines and any appropriate distribution system.

A.2.1.11 Bulk delivery concentrate

The delivery of concentrate in bulk containers has become commonplace in some countries. This practice carries with it responsibilities for both the user and the manufacturer. When bulk deliveries of liquid concentrate are made, the product is dispensed in a large holding tank and the original labelling is lost. The maintenance of the holding tank is normally the responsibility of the user. The tank and its associated piping should be periodically cleaned and disinfected according to standard procedures. Care should 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. It was decided that the point of transfer of the concentrate solution is the point at which the responsibility for its labelling and integrity transfers to the user. Written procedures should define this exchange.

When liquid concentrate is delivered to the end user in bulk form, the user should 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 should be made.

A.2.1.12 Concentrate generator systems

As technology progresses, some manufacturers produce concentrate preparation systems that prepare a solution for use by the dialysis machine. It was decided that such systems should be added to this International Standard. Those systems create 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. Because the connectors could vary, it was considered necessary to state with which machines the canisters could be used.

Concentrate generator systems cannot be used with some proportioning systems, such as 36,83 systems where the sodium bicarbonate is combined with sodium chloride, since there is no way of knowing that the dissolution rates of sodium bicarbonate and sodium chloride will be the same.

It is the machine manufacturer's responsibility to design and manufacture the dialysis machine, including all necessary safety checks, to ensure that the system will deliver a safe and effective dialysis fluid to the dialyser. Where necessary, filtering should be provided to prevent undissolved powder from entering the dialysis fluid stream.

A.2.2 Manufacturing equipment

A.2.2.1 General

Non-toxicity 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 can be toxic in this application (e.g. copper leaches from copper conduits, especially in the presence of low pH, which can arise when a deionizer is exhausted). Other materials have been documented as being hazardous to the patient (e.g. copper, brass, zinc, galvanized material, and aluminium), and they should also be avoided. Some well-recognized non-toxic 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. A risk analysis according to ISO 14971 should be used to assess the suitability and biocompatibility of materials based on existing data. If that analysis suggests the need

for additional testing, that testing should be based on the approaches outlined in the ISO 10993 series of standards. Users of this International Standard should be aware of the requirements of those standards.

A.2.2.2 Endotoxin levels

The endotoxin concentration in bicarbonate concentrate is required to be such that, when it is mixed with water in the appropriate proportions, the resulting dialysis fluid meets the quality requirements of ISO 11663. Because endotoxin in the final dialysis fluid could be derived from both the concentrate and the water, the water used to dilute the concentrate for endotoxin testing should contain the maximum allowable level of endotoxin allowed under ISO 13959, to allow the final dialysis fluid to meet the requirements of ISO 11663 under worst case conditions. That implies that the water used to mix the powder for testing could contain 0,25 EU/ml of endotoxin. It is not practical to prepare water containing exactly that level of endotoxin, also, the assayed endotoxin concentration could change with the addition of ions from the concentrate (aggregate formation).

A.3 Labelling

A.3.1 General

Existing regulations establish general requirements for the labelling of all medical devices, including information, such as name and address of manufacturer and lot number. It was decided, however, that redundancy of these requirements was preferable to omission and the requirement that some of the same information already mandated by other regulations be included.

A.3.2 Labelling requirements for liquid concentrate

This specialized information provides for the proper use of concentrate for haemodialysis supplied in an aqueous form. Requiring a precaution against excessive cold, as well as requiring a precaution against excessive heat was considered 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, preventing inadvertent use of the wrong solution caused by similarities in containers was considered especially important.

There are no known instances of pyrogenic reactions caused by pyrogens in the acid part of the concentrate. There is also the possibility that acid concentrate will deactivate pyrogens because of its low pH.

A.3.3 Labelling requirements for powder concentrate

Bicarbonate concentrate is known to support bacterial growth. Other data support 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 label should include instructions to avoid exposure to excessive temperature and to keep the container tightly sealed until use. When bicarbonate is used, a warning should be included noting that water containing an otherwise acceptable number of bacteria will be entering an environment which can support bacterial growth and, therefore, procedures should 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, according to the manufacturer's instructions.

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2) Withdrawn.

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