International Standard

ISO 23500-4

Second edition
2024-04

Preparation and quality management of fluids for haemodialysis and related therapies —

Part 4: Concentrates for haemodialysis and related therapies

Préparation et management de la qualité des liquides d'hémodialyse et de thérapies annexes —

Partie 4: Concentrés pour hémodialyse et thérapies apparentées

Reference number
ISO 23500-4:2024(en)

ISO copyright office
CP 401 • Ch. de Blandonnet 8
CH-1214 Vernier, Geneva
Phone: +41 22 749 01 11
Email: copyright@iso.org
Website: www.iso.org

Published in Switzerland

Contents

Page

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 document 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).

ISO draws attention to the possibility that the implementation of this document may involve the use of (a) patent(s). ISO takes no position concerning the evidence, validity or applicability of any claimed patent rights in respect thereof. As of the date of publication of this document, ISO had not received notice of (a) patent(s) which may be required to implement this document. However, implementers are cautioned that this may not represent the latest information, which may be obtained from the patent database available at www.iso.org/patents. ISO shall not be held responsible for identifying any or all such patent rights.

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

For an explanation of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT), see www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 150, *Implants for surgery*, Subcommittee SC 2, *Cardiovascular implants and extracorporeal systems*, in collaboration with the European Committee for Standardization (CEN) Technical Committee CEN/TC 205, *Non-active medical devices,* in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

This second edition cancels and replaces the first edition (ISO 23500-4:2019), which has been technically revised.

The main changes are as follows:

— alternatives to classic microbial analytical methods [endotoxin testing using rFC (tp)] have been incorporated;

— further clarifications on the use of concentrates spikes and containers have been added.

A list of all parts of the ISO 23500 series can be found on the ISO website.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

The requirements established in this document will help ensure the effective, safe performance of haemodialysis concentrates and related materials. Haemodialysis concentrates are a mixture of chemicals and water, or chemicals in the form of dry powder or other highly concentrated media, which are delivered to the end user to make dialysis fluid used to perform haemodialysis and related therapies. In this document, the dialysis fluid made by the end user mixing haemodialysis concentrate and water of the quality given in ISO 23500-3 is discussed to help clarify the requirements for manufacturing concentrates. Therefore, it is recommended to refer to ISO 23500-3 along with this document.

This document reflects the conscientious efforts of concerned physicians, clinical engineers, nurses, dialysis technicians and dialysis patients, in consultation with device manufacturers and regulatory agency representatives to develop a standard for performance levels. 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 are merged.

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, Furthermore, label requirements for dialysis fluid are placed on the labelling of the concentrate, it is the user's responsibility to ensure proper use.

The rationale for the development of this document is given in Annex A.

Preparation and quality management of fluids for haemodialysis and related therapies —

Part 4: Concentrates for haemodialysis and related therapies

1 Scope

This document specifies the chemical and microbiological requirements for concentrates used for haemodialysis and related therapies and applies to the manufacturer of such concentrates.

This document is applicable to:

— concentrates in both liquid and powder forms;

— additives, also called spikes, which are chemicals that can be added to the concentrate to supplement or increase the concentration of one or more of the existing ions in the concentrate and thus in the final dialysis fluid;

— equipment used to mix acid and bicarbonate powders into concentrate at the user's facility.

This document does not apply to:

— concentrates prepared from pre-packaged salts and water at a dialysis facility for use in that facility;

— pre-packaged and sterile dialysis fluid;

— sorbent dialysis fluid regeneration systems that regenerate and recirculate small volumes of the dialysis fluid;

— equipment to perform patient treatment; this is addressed IEC 60601-2-16.

This document does not cover the dialysis fluid that is used to clinically dialyse patients. Dialysis fluid is covered in ISO 23500-5. 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.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 23500-1, *Preparation and quality management of fluids for haemodialysis and related therapies — Part 1: General requirements*

ISO 23500-3, *Preparation and quality management of fluids for haemodialysis and related therapies — Part 3: Water for haemodialysis and related therapies*

ISO 23500-5, *Preparation and quality management of fluids for haemodialysis and related therapies — Part 5: Quality of dialysis fluid for haemodialysis and related therapies*

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 terms and definitions given in ISO 23500-1 and the following apply.

ISO and IEC maintain terminology databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at https://www.electropedia.org/

3.1
bicarbonate dialysis fluid
dialysis fluid containing physiological or higher concentrations of bicarbonate

Note 1 to entry: Dry sodium bicarbonate, without added sodium chloride, is also used in *concentrate generators* (3.3) to produce a concentrated solution of sodium bicarbonate used by the dialysis machine to make dialysis fluid.

3.2
concentrate mixer
mixer for the preparation of dialysis concentrate for dialysis fluid at a dialysis facility

3.3
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.

4 Requirements

4.1 Concentrates

4.1.1 Physical state

4.1.1.1 General

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

4.1.1.2 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. 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. Where concentrates include non-traditional constituents, such as antioxidants and iron compounds, these constituents shall be present at nominal concentrations with ±5 % tolerances. 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 and glucose. New concentrates are available which include additional chemicals or 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 information and the substitute chemicals shall be present at nominal concentrations with ±5 % tolerance. If alternate, locally approved tolerances are used, the tolerances shall be similarly stated and the rationale for their use documented.

It is essential that the actual concentrations of the solutes contained in the concentrate be as close as possible to the labelled amount since the final composition of the dialysis fluid will be subject to cumulative variability from other sources within the process of dialysis fluid delivery (such as, but not limited to, laboratory testing, mixing process or proportioning, dialysis water).

4.1.1.3 Solute concentrations based on 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 concentrate shall meet the requirements of 4.1.1.1.

4.1.2 Water

The quality of water used in the manufacture of the concentrate shall be in accordance with ISO 23500-3.

4.1.3 Bacteriology of concentrates

4.1.3.1 Bacteriology of acid concentrates

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

4.1.3.2 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 23500-5, when used in accordance with 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 23500-5, when used in accordance with the manufacturer's instructions.

4.1.4 Endotoxin levels

The concentrate shall be formulated and packaged using a process validated to produce dialysis fluid meeting the endotoxin requirements of ISO 23500-5 or the applicable pharmacopoeia when used in accordance with the manufacturer's instructions.

4.1.5 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 in accordance with the manufacturer's instructions, it produces liquid concentrate that meets the requirements of 4.1.1.1. 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.

4.1.6 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 can 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.

4.1.7 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.

4.1.8 Additives — "Spikes"

The use of concentrate additives such as potassium chloride in a canister is not recommended. Due to differences in density, homogeneous mixing is made more difficult and there is a risk of "island formation", i.e. areas with a high concentration of the concentrate additive. If the dialysis machine aspirates such areas, this can lead to a serious patient risk.

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

NOTE The use of additives is not approved in some countries.

4.1.9 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 3).

Dialysis concentrates in canisters are usually intended for single use by the manufacturer and labelled accordingly. If not completely used, sometimes canisters are reused by the user. In those cases, the user is liable for any damage to health resulting from the reuse.

If the container or cannister is of a type which is suitable for use in multiple treatment sessions, an appropriate risk control measure shall be introduced so that the use of the container and its contents beyond the initial use does not introduce risks to the patient.

The following risks exist, among others:

— cross-contamination due to use of a contaminated canister contents with another patient, e.g. if the canister was not used for the specific patient;

— changes in the chemical composition or the microbiological contamination due to storage, e.g. beyond the next patient treatment day;

— contamination, evaporation and change in concentration of contents arising from incorrect re sealing of the container.

4.1.10 Bulk-delivered concentrate

When concentrate is delivered in bulk form, the responsibility for ensuring conformity with this document 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.

4.1.11 Concentrate generators

Concentrate generator systems include systems that mix powder, or 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 specified 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 metal or aluminium.

4.3 Systems for bulk 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, residual levels can be determined by the Hantzsch reaction, Schiff's reagent, or by an equivalent test. Residual levels shall not exceed 3 mg/l.

NOTE Local requirements can apply.

When ozone is used, the residual level shall be less than 0,1 mg/l; when sodium hypochlorite is used, test strips with a minimum indication of 0 mg/l shall be used.

If other chemicals are used, appropriate testing in accordance with the manufacturer’s recommendations shall be used.

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 a chemical disinfectant, such as 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 can 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, can be used.

4.3.6 Ultraviolet irradiators

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

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

b) the ultraviolet irradiator shall provide a dose of radiant energy of 160 J/m^2 if it is fitted with a calibrated ultraviolet intensity meter, otherwise it shall provide a dose of radiant energy of 300 J/m^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 microbial proliferation and biofilm formation that can contaminate susceptible concentrates. Frequent disinfection of bicarbonate concentrate distribution systems is one way to minimize microbial 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 specifies test methods by which conformity with the requirements of Clause 4 shall 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 are permitted, provided it has been demonstrated that such methods have been appropriately validated and are comparable to the cited methods.

5.2 Concentrates

5.2.1 Physical state

Conformity with the requirements of 4.1.1 shall be determined by visual inspection.

5.2.2 Solute concentrations

5.2.2.1 Liquid solute concentrations

Conformity with the requirements of 4.1.1.1 for calcium, potassium, magnesium and sodium shall be determined by using methods described by the American Public Health Association,[7] the Environmental Protection Agency,[8] 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.

Conformity with the requirements of 4.1.1.1 for new and non-traditional concentrate constituents shall be determined by using appropriate and validated analytical methods.

The maximum contaminant levels referred to in ISO 23500-3 shall be used as a reference for dialysis water.

Conformity with the requirements for the contents of the dialysis fluid shall be determined as described in Table 1. Other test methods are permitted, provided it has been demonstrated that such methods have been appropriately validated and are comparable 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, 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

Conformity with the water quality requirements of 4.1.2 shall be determined by using methods referenced in ISO 23500-3.

5.2.4 Microbial contaminant test methods for bicarbonate concentrates

To ensure conformity with 4.1.3.2, the samples for total viable counts should be processed and tested using the membrane filter technique or other validated standard test methods such as spread plate or pour plate technique. The calibrated loop technique shall not be used.

Recommended methods are shown in Table 2. Such methods provide only a relative indication of the microbial bioburden rather than an absolute measure. The manufacturer should determine which of these methodologies is appropriate for the circumstance, taking into account the advantages of each methodology.

The decision to use longer incubation times, should be made after balancing the need for timely information and the type of corrective actions required when alert or action level is exceeded with the ability to recover the microorganisms of interest. The advantages gained by incubating for longer times namely recovery of injured microorganisms, slow growers, or more fastidious microorganisms, should be balanced against the need to have a timely investigation and take corrective action, as well as the ability of these microorganisms to detrimentally affect products or processes" (e.g. patient safety).

Salt tolerance studies have shown that optimal growth of organisms found in bicarbonate concentrate occurs when the aqueous sodium chloride concentration is approximately 3 % to 6 %. Consequently, the usage of a low-salt medium, such as Reasoner's agar no. 2 (R2A) or tryptone glucose extract agar (TGEA), should be supplemented with 4 % sodium bicarbonate.

Currently, there is no requirement for routine surveillance for the presence of yeasts and filamentous fungi. If such information is required, the culture media shall be Sabouraud or malt extract agar (MEA). Other media, incubation temperatures and incubation times are permitted provided it has been demonstrated that such methods have been appropriately validated and are comparable to the cited methods. Blood or chocolate agar shall not be used.

The microbiological purity of packaged liquid concentrates and dry powder cartridges is the responsibility of the manufacturer. Surveillance of bicarbonate concentrate produced at a dialysis facility from powder and water, though not required routinely, can be undertaken as part of a troubleshooting investigation.

Table 2 — Culture techniques used in bicarbonate concentrate

Culture medium	Incubation temperature	Incubation time
TGEA[a]	17 °C to 23 °C	7 d
R2A[a]	17 °C to 23 °C	7 d
Tryptic soy agar (TSA)[b]	35 °C to 37 °C	48 h

[a] The sodium content of Reasoner's 2A and TGEA is insufficient for use in culturing bicarbonate concentrate and should be supplemented with 4 % sodium bicarbonate.

[b] The sodium content of TSA is sufficient for use in culturing bicarbonate concentrate without supplementation.

5.2.5 Endotoxin levels

Conformity with the requirements of 4.1.4 can be determined by the Limulus amoebocyte lysate (LAL) test for endotoxins.

The detection of bacterial endotoxins, which originate from gram-negative bacteria, is mainly carried out using the amoebocyte lysate (LAL), which is obtained from horseshoe crab blood (*Limulus polyphemus*

or *Tachypleus tridentatus*). The corresponding chapters have been harmonized between the European Pharmacopoeia ((EP) 2.6.14.)[9], the Pharmacopoeia of the United States-National Formulary, (<85>)[10] and the Japanese Pharmacopoeia (4.01)[11].

The LAL test is based on the humoral coagulation cascade of the horseshoe crab *Limulus polyphemus*. The first enzyme in this coagulation cascade reacts with endotoxin and is called Factor C. This factor is now produced recombinantly (biotechnologically) and offered as the rFC test by several manufacturers for the determination of bacterial endotoxins. Compared to the LAL test, the rFC test has proven to be at least as sensitive and reliable, but less susceptible to certain interfering factors and batch fluctuations. Due to biotechnological production, no live animals are required as blood donors.

This new method has been incorporated into the European Pharmacopoeia (2.6.32)[12] and it is planned to be included into the United States Pharmacopoeia-National Formulary (<1085.1>)[13].

5.2.6 Fill quantity

Conformity with the requirements of 4.1.5 can be determined by the use of appropriate volumetric or gravimetric techniques.

5.2.7 Chemical grade

Purity of chemicals as specified in 4.1.6 can be determined by test methods outlined in the appropriate pharmacopoeia.

5.2.8 Particulates

Conformity with the requirements of 4.1.7 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"

Conformity with 4.1.8 can 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 can 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

Conformity with the requirements of 4.1.9 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

Conformity with the requirements of 4.1.10 can be determined by review of the delivery procedures.

5.2.12 Concentrate generators

Conformity with 4.1.11 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 can modify his equipment to use another manufacturer's concentrate generator system. When this is done, 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

Conformity 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

Conformity 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 a comparable 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 in accordance with the test manufacturer's instructions.

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

5.4.3.2 System lock out

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

5.4.4 Safety requirements

Conformity with 4.3.4 can be determined by inspection.

5.4.5 Bulk storage tanks

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

5.4.6 Ultraviolet irradiators

Conformity 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, 5.2.5 and 5.3.

5.4.8 Electrical safety requirements

Conformity with the requirements of 4.3.8 can be determined using the tests found in IEC 60601-1, as appropriate.

6 Labelling

6.1 General

The term "labelling" in this document 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 specified in ISO 15223-1 and ISO 7000 can be used where appropriate.

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 1 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) 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 millimoles per litre (mmol/l);

the chemical concentration of the final dialysis fluid shall be placed on the acid concentrate label;

NOTE 2 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 the storage, handling, and transportation requirements; for example: “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 are 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 microbial 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 23500-3 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 Clause A.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 microbial 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 23500-5 when used in a properly maintained system.

   3) Liquid concentrate labelling can include geometric symbols (see Table 3) 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 means to differentiate between acid and bicarbonate. If a concentrate contains no potassium or no calcium, this information 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 and handling 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 can include geometric symbols (see Table 3) 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 microbial contamination, as well as, appropriate warnings that residual bicarbonate concentrate, uncleaned mixing tanks, and mixing systems will support microbial growth.

f) Dialysis water should be used to mix the concentrate.

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 can modify their 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, among others).

Table 3 — Symbols for concentrate container system: Concentrate types

Designation	Total mix[b,c]	Acid mix[d,e]	Bicarbonate mix[f,g]	Symbol
	1 + 1,23 + 32,77	1 + 34	1 + 27,46	 Square
	1 + 1,83 + 34	1 + 35,83	1 + 19,13	 Circle
	1 + 1,72 + 42,28	1 + 44	1 + 25,16	 Triangle
	1 + 1,1 + 34	1 + 35,1	1 + 31,8	 Diamond
Other[a] (new)	TBD[a]	TBD[a]	TBD[a]	TBD[a]

[a] Any new mix 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] The total mix proportions are expressed as the sum of the acid concentrate, the bicarbonate concentrate and the water mix proportions.

[c] There can be minor differences in mix proportions within each concentrate type; for example, 1 + 1,18 + 32,82 and 1 + 1,26 + 32,74 instead of 1 + 1,23 + 32,77, and 1 + 1,58 + 42,42 instead of 1 + 1,72 + 42,28.

[d] The acid mix proportions are expressed as the sum of the acid concentrate, and the bicarbonate concentrate and water mix proportions.

[e] Mix proportions of 1:34 and 1:44 can be used instead of 1 + 34, and 1 + 44.

[f] The bicarbonate mix proportions are expressed as the sum of the bicarbonate concentrate, and the acid concentrate and water mix proportions.

[g] Bicarbonate mix proportions are based on 8,4 % (84 g/l) sodium bicarbonate solution (1 000 mmol/l). Other solutions can be used clinically and their use can result in a different mix proportions.

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 user;

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 can 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 surveillance schedules, troubleshooting 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 document

A.1 General

The items included within the scope of this document are the reagents and devices required to manufacture haemodialysis concentrate. This document 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 document.

Concentrate solutions whether liquid or dry, whether general or specific, are prepared and put into use as dialysis fluid by the user; this critical final step is not under the control of the manufacturer. Whereas the manufacturer has the responsibility to ensure that the concentrate solutions are manufactured in accordance with the requirements of this document, the facility using and preparing dialysis fluid from the concentrated solutions has the responsibility to ensure that its professional staff (physicians nursing and technical staff) are adequately instructed, trained and informed to ensure that the concentrate solutions are used in a safe and effective manner.

Haemodialysis is a complex procedure whose aim is to normalize chemical abnormalities and control acidosis arising from renal insufficiency. Many different concentrated solutions in liquid or powder form are available commercially. They are used with a variety of proportioning and mixing systems, the aim being to deliver a dialysis fluid most appropriate to the patient's clinical requirements, to achieve normalization of chemical abnormalities and to optimize acid base balance.

Dialysis fluid is produced by the mixing of three components: the acid concentrate, the bicarbonate concentrate and dialysis water, the latter meeting requirements detailed in ISO 23500-3. This mixing can be done by the use of proportioning systems intended for single patient use or performed centrally with the fluid thus produced supplied to the bedside.

Whereas in some dialysis units, a single formulation can be used for all patients receiving treatment, increasingly, the dialysis fluid electrolyte and buffer content is individualized and 'prescribed' for the patient, whereby the physician prescribes the individual sodium or bicarbonate buffer content for the patient. Such prescription affords the patient a high degree of treatment tolerability.

The electrolyte and buffer content of the dialysis fluid is dependent upon the acid and bicarbonate mix ratio governed by the proportioning system or dialysis machine in use and the concentrate type. Minor differences in the mix ratio within each of the concentrate types can exist as indicated in Table 3 and users should consult the dialysis machine manual for the exact proportioning ratio to ensure that the dialysis fluid produced meets the clinically prescribed electrolyte and buffer concentration.

One of the functions of the dialysis fluid is to correct metabolic acidosis present in patients undergoing dialysis treatment. Because bicarbonate is the most important buffer in the body, the choice of bicarbonate as a dialytic buffer is a logical consequence. Current haemodialysis treatments utilize proportioning or mixing technology which uses two separate concentrates mixed with dialysis water — the acid concentrate and the bicarbonate concentrate. The acid concentrate, sometimes referred to as acidified concentrate as it contains small amounts of acid, also contains most of the electrolytes. The bicarbonate concentrate contains sodium bicarbonate. The use of two separate concentrates is necessary to avoid the precipitation of carbonate formed by bicarbonate coming into contact with divalent ions in particular calcium and magnesium, which if formed presents major technical problems.

Depending on the type of acidified concentrate in use, the acid component may be in the form of sodium acetate, sodium di-acetate, citric acid or lactate. Acetate and lactate are metabolized to bicarbonate in a 1:1

ratio, while citric acid generates bicarbonate in a 3:1 molar ratio. In selecting the dialysis fluid bicarbonate prescription, the physician should consider all sources of buffer delivered to the patient during the dialysis treatment, including the bicarbonate in the bicarbonate concentrate, the acetate, citrate or lactate in the acid concentrate which, when metabolized form bicarbonate. In selecting the bicarbonate prescription, the physician should additionally consider the patient's nutritional status assessed by history, physical examination, anthropometrics, serum albumin and protein nitrogen appearance, since individuals whose metabolism results in a small acid load are at higher risk of developing metabolic alkalosis following treatment. Decisions regarding the bicarbonate prescription should also take into account changes in serum potassium, magnesium and calcium concentrations during dialysis, and the presence and severity of heart disease.

To achieve the clinically required dialysis fluid composition in respect of electrolyte and buffer content, users should pay attention to ensure that the mix ratios used are appropriate and intended for the proportioning system or dialysis machine in use. Recognition and application of appropriate concentrates to produce the desired dialysis fluid is the responsibility of the end user as at the present time, adequate surveillance does not exist which ensures that mismatched concentrates do not produce a final dialysis fluid of proper total conductivity but of improper composition. The user is therefore cautioned not to rely solely on conductivity measurements to ensure safety, but to consider all relevant factors, including pH.

The final step of using or selecting concentrate solutions in the preparation of dialysis fluid is not under the control of the manufacturer. Therefore, within this document, an attempt has been made to set out requirements (including both manufacturer and user responsibility) to ensure correct formulation and use. Within this context, stringent requirements have been reserved for specifications which if not complied with can pose serious threats to the patient. More liberal standards have been chosen when the risk to the patient is low.

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 the utilization of two concentrates because concentrated calcium and bicarbonate will precipitate when combined. Technology for dual proportioning is widely available, however manufacturers of equipment have not adopted a single unified approach, consequently, different systems proportion at different ratios (e.g. 35X, 36,83X, 45X). Systems can use dry powder made into a concentrated solution by the dialysis fluid delivery system. Some concentrates contain sodium chloride in the bicarbonate solution, requiring a corresponding adjustment in the parallel counterpart acid concentrate, while others can use sodium acetate, sodium diacetate or citric acid in the acid concentrate, necessitating careful attention to bicarbonate that the metabolism of these compounds generates. When selecting a dialysis fluid formulation, base components and their role in the acid base correction need to be clearly understood.

At the present time, adequate surveillance does not exist which ensures that mismatched concentrates do not produce a final dialysis fluid of proper total conductivity but of improper composition. The user is therefore 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.

Standards for bicarbonate dialysis fluid delivery systems thus should address both proportioning and surveillance 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 electrodes that the fluid path contains. 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 surveillance 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 can 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 since the final composition of the dialysis fluid will be subject to cumulative variability from other sources within the process of dialysis fluid delivery (including but not confined to laboratory testing, mixing process or proportioning, dialysis water). At present it is not practical to accurately specify and measure relative contributions from each of these potential sources and to adjust for them.

Although excessive variations can be hazardous to the patient, tolerances of less than 5 % for glucose and the minor cations corresponding to a variation of 0,1 mEq/l for the minor cations or of 5 mg/dl for glucose can be consistently achieved. 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 23500-3 were referenced.

A.2.1.5 Microbiology of bicarbonate concentrates

Bicarbonate concentrates have been shown to support microbial growth and to provide another bioburden source capable of rapid increase after dilution.[14]-[15] Recognition of this hazard requires additional precautions in preparation, containers, storage and prompt use to avoid excess growth of haloduric organisms. This document provides acceptable methods described in 5.2.4 for microbiological surveillance. It should be noted however that the methods do not provide a measure of the absolute microbial burden but are only a relative indicator of the bioburden. Other methods can be used, provided it has been demonstrated that such methods have been appropriately validated and are comparable to the cited methods.

Currently, there is no requirement to specifically undertake testing for the presence of yeast and filamentous fungi; it should be recognized that such organisms frequently coexist with other microbial contaminants.

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 can 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