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**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*

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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](http://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](http://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 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](http://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*.

This first edition cancels and replaces ISO 13958:2014, which has been technically revised. The main changes compared to the previous edition are as follows:

- The document forms part of a revised and renumbered series dealing with the preparation and quality management of fluids for haemodialysis and related therapies. The series comprise ISO 23500-1 (previously ISO 23500), ISO 23500-2, (previously ISO 26722), ISO 23500-3, (previously ISO 13959), ISO 23500-4, (previously ISO 13958), and ISO 23500-5, (previously ISO 11663).

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](http://www.iso.org/members.html).

## Introduction

The requirements and goals established by this document will help ensure the effective, safe performance of haemodialysis concentrates and related materials. 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 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 shall be merged.

The rationale for the development of this document is given in informative [Annex A](#).

Throughout this document, requirements and recommendations are made to use ISO-quality water. Therefore, it is recommended to refer to ISO 23500-3 along with this document.

For the purpose of this document, “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.

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

## Part 4: Concentrates for haemodialysis and related therapies

### 1 Scope

This document specifies minimum requirements for concentrates used for haemodialysis and related therapies.

This document is addressed to the manufacturer of such concentrates. In several instances in this document, the dialysis fluid is addressed, 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 document includes concentrates in both liquid and powder forms. It also includes 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.

This document also specifies requirements for equipment used to mix acid and bicarbonate powders into concentrate at the user's facility.

Concentrates prepared from pre-packaged salts and water at a dialysis facility for use in that facility are excluded from the scope of this document. Although references to dialysis fluid appear herein, this document does not address dialysis fluid as made by the end user. This document also excludes requirements for the surveillance frequency of water purity used for the making of dialysis fluid by the dialysis facility. This document does not address bags of sterile dialysis fluid or sorbent dialysis fluid regeneration systems that regenerate and recirculate small volumes of the dialysis fluid.

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.

This document does not cover haemodialysis equipment, which is addressed in IEC 60601-2-16:2012.

### 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 terminological databases for use in standardization at the following addresses:

- ISO Online browsing platform: available at <https://www.iso.org/obp>
- IEC Electropedia: available at <http://www.electropedia.org/>

#### 3.1

##### **batch system**

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

Note 1 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.

#### 3.2

##### **bicarbonate dialysis fluid**

dialysis fluid containing physiological or higher concentrations of bicarbonate

#### 3.3

##### **concentrate mixer**

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

### 4 Requirements

#### 4.1 Concentrates

##### 4.1.1 Physical state

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).

##### 4.1.1.1 Liquid solute concentrations

All electrolytes identified on the label shall be present within  $\pm 5\%$  or  $\pm 0,1$  mEq/l (expressed as dialysis fluid concentrations), whichever is greater, of the stated concentration, with the exception of sodium, which shall be present within  $\pm 2,5\%$  of the labelled concentration or shall be present according to approved specifications by the local regulations. If used, glucose shall be present within  $\pm 5\%$  or  $\pm 0,05$  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  $\pm 5\%$  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, 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 and the substitute chemicals shall be present at nominal concentrations

with  $\pm 5\%$  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.

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 confined to laboratory testing, mixing process or proportioning, dialysis water).

#### 4.1.1.2 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 final 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 bacterial growth and as such, acid concentrate need not be tested for bacterial 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 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 23500-5, when used according to 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 according to 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 according to 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  $\geq 100\%$  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”

If additives are supplied, the concentration, when properly diluted with water or concentrate, shall yield values within  $\pm 5\%$  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](#)).

#### 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 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 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, the residual level shall be less than 3 mg/l; when sodium hypochlorite is used, the residual level shall be as specified per the manufacturer's instructions; 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 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 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 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<sup>2</sup> if it is fitted with a calibrated ultraviolet intensity meter, otherwise it shall provide a dose of radiant energy of 30 mW·s/cm<sup>2</sup>;
- 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 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[5], methods referenced by the U.S. Environmental Protection Agency[6], 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.

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 <sub>2</sub>   |
| 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

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 bacterial 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.

According to the United States Pharmacopeia, “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][14].

Salt tolerance studies have shown that optimal growth of organisms found in bicarbonate concentrate occurred when the sodium chloride concentration was approximately 3 % to 6 %. Consequently, the usage of a low-salt medium, such as Reasoner's 2A or 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 |
|--|------------------------|-----------------|
| Tryptone Glucose Extract Agar (TGEA) <sup>a</sup>  | 17 °C to 23 °C         | 7 d             |
| Reasoner's Agar no. 2 (R2A) <sup>a</sup>   | 17 °C to 23 °C         | 7 d             |
| Tryptic Soy Agar (TSA) <sup>b</sup>  | 35 °C to 37 °C         | 48 h            |
| <p><sup>a</sup> 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.</p> <p><sup>b</sup> The sodium content of TSA is sufficient for use in culturing bicarbonate concentrate without supplementation. The use of TSA has been only validated for measurement of standard dialysis fluid.</p> |                        |                 |

**5.2.5 Endotoxin levels**

Conformity with the requirements of 4.1.4 can be determined by the LAL test for endotoxins. Other test methods can be used provided it has been demonstrated that such methods have been appropriately validated and are comparable to the cited methods.

**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  $\pm 5\%$  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  $\pm 5\%$  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 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

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 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.

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 or IEC 61010-1 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 can be used where appropriate.

NOTE 1 See ISO 15223-1 *Medical devices — Symbols to be used with medical device labels, labelling and information to be supplied — Part 1: General requirements*.

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 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 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 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 [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 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 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 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 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 bacterial contamination. Also, appropriate warnings that residual bicarbonate concentrate, uncleaned mixing tanks, and mixing systems will support bacterial 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) Dilution 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, among others.).

**Table 3 — Symbols for concentrate container system: concentrate types**

| Designation                          |  |  |  |  | Other <sup>a</sup><br>(new) |
|--------------------------------------|---|---|--|---|-----------------------------|
| <b>Total Mix<sup>b,c</sup></b>       | 1+1,23+32,77  | 1+1,83+34   | 1+1,72+42,28   | 1+1,1+34  | TBD <sup>a</sup>            |
| <b>Acid mix<sup>d,e</sup></b>        | 1+34  | 1+35,83   | 1+44   | 1+35,1  | TBD <sup>a</sup>            |
| <b>Bicarbonate Mix<sup>f,g</sup></b> | 1+27,46   | 1+19,13   | 1+25,16  | 1+31,8  | TBD <sup>a</sup>            |
| <b>Symbol</b>                        | Square □  | Circle ○  | Triangle △   | Diamond ◇   | TBD <sup>a</sup>            |

<sup>a</sup> 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).

<sup>b</sup> Acid concentrate +bicarbonate concentrate +water.

<sup>c</sup> There can be minor differences in mix proportions 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.

<sup>d</sup> Acid concentrate + bicarbonate concentrate+ water.

<sup>e</sup> The acid mix proportions can also be expressed as acid concentrate + (bicarbonate concentrate +water); Dilution Ratio 1:34 and 1:44 can be used instead of, 1 + 34, and 1 + 44.

<sup>f</sup> The bicarbonate mix proportions can also be expressed as bicarbonate concentrate + (acid concentrate + water).

<sup>g</sup> Bicarbonate mix ratios are based on 8,4 % sodium bicarbonate solution (1 000 mmol/l). Other solutions can be used clinically and their use can 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 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 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 surveillance 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.

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## Annex A (informative)

### Rationale for the development and provisions of this document

#### A.1 Scope

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 standard, 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<sup>[7][8][9]</sup>.

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 23500-3:2019. This mixing can be 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<sup>[7][8][9]</sup>.

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<sup>[11]</sup>.

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<sup>[10]</sup>. 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 give consideration to 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 standard, an attempt has been made to set out requirements including both manufacturer and user responsibility in ensuring 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 could 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 23500-3:2019 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<sup>[12][13]</sup>. 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 bacterial 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, and it should be recognized that such organisms frequently coexist with other microbial contaminants.