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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).

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

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

For an explanation 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*.

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.

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.

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

Most concentrates are manufactured with standard traditional chemicals such as sodium chloride, potassium chloride, magnesium chloride, calcium chloride, acetic acid, 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 ± 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 ≥ 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 ± 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.