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International Standard

ISO/FDIS 23500-4

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

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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).

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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 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 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 confined 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.