SLOVENSKI STANDARD
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Priprava in vodenje kakovosti tekočin za hemodializo in podobne terapije - 1. del: Splošne zahteve (ISO/DIS 23500-1:2022)

Preparation and quality management of fluids for haemodialysis and related therapies - Part 1: General requirements (ISO/DIS 23500-1:2022)

Herstellung und Qualitätsmanagement von Flüssigkeiten für die Hämodialyse und verwandte Therapien - Teil 1: Allgemeine Anforderungen (ISO/DIS 23500-1:2022)

Préparation et management de la qualité des liquides d'hémodialyse et de thérapies annexes - Partie 1: Exigences générales (ISO/DIS 23500-1:2022)

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

Part 1: General requirements

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

Partie 1: Exigences générales

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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 second edition cancels and replaces ISO 23500-1:2019, which has been technically revised. The main changes compared to the previous edition are:

— The use of WHO Drinking Water Guideline as the main drinking water quality reference instead of the US EPA or other European standards, and a review of the list of chemical contaminants of other trace elements in dialysis water. After considerable discussion, it was decided to omit thallium from the list of contaminants since no studies have reported data to indicate that this contaminant is of particular concern in the haemodialysis setting .

— Incorporation of alternative water treatment technologies (e.g. reverse osmosis pre-treatment with ultrafiltration).

— Addition of a new Annex (H) providing clarification of the different water quality monitoring approaches (online versus offline monitoring).

— Updating of the microbiological analytic methods to include; endotoxin testing using rFC (tp); Flow Cytometry; Autofluorescence and Rapid Tests (e.g. ATP)].

— Additon of a new Annex (I) providing guidance on risk assessment.

— Introduction of specific terms for the verification of water treatment system design and performance, e.g. Retrospective validation, Initial validation and Revalidation

— Further guidance on technical needs after typical technical interventions (Annex E.4)

A list of all parts in 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

This document is the base standard for a number of other standards dealing with water treatment and the production of dialysis fluid (ISO 23500 series).

The objective of the ISO 23500 series is to provide users with guidance for handling water and concentrates and for the production and quality oversight of dialysis fluid used for haemodialysis. The need for such guidance is based on the critical role of dialysis fluid quality in providing safe and effective haemodialysis, and the recognition that day-to-day dialysis fluid quality is under the control of the healthcare professionals who deliver dialysis therapy.

Annex A provides further information on the rationale for the development and provisions of this document.

The equipment used in the various stages of dialysis fluid preparation is generally obtained from specialized vendors. Dialysis practitioners are generally responsible for maintaining that equipment following its installation. Therefore, this document provides guidance on quality oversight and maintenance of the equipment to ensure that dialysis fluid quality is acceptable at all times. At various places throughout this International Standard, the user is advised to follow the manufacturer's instructions regarding the operation and maintenance of equipment. In those instances in which the equipment is not obtained from a specialized vendor, it is the responsibility of the user to validate the performance of the equipment in the haemodialysis setting and to ensure that appropriate operating and maintenance manuals are available.

Annex B to this document provides further information on the system components that are used for water treatment, concentrate, and dialysis fluid preparation at a dialysis facility. These descriptions are intended to provide the user with a basis for understanding why certain equipment might be required and how it should be configured; they are not intended as detailed design standards. Requirements for water treatment equipment are provided in ISO 23500-2.

Increasingly, self-contained, integrated systems designed and validated to produce water and dialysis fluid are becoming available and used clinically. This document applies to systems assembled from individual components. Consequently, some of the requirements in ISO 23500-1 and ISO 23500-2 might not apply to integrated systems, however such systems are required to comply with the requirements of ISO 23500-3, ISO 23500-4, and ISO 23500-5. In order to ensure conformity when using such systems, adherence to the manufacturer's instructions regarding the operation, testing, and maintenance of such systems is required to ensure that the system is being operated under the validated conditions.

This document reflects the conscientious efforts of healthcare professionals, patients, and medical device manufacturers to develop recommendations for handling water and concentrates and for the production and surveillance of dialysis fluid for haemodialysis and protecting haemodialysis patients from adverse effects arising from known chemical and microbial contaminants that might be found in improperly prepared dialysis fluid. Annexes F and G provide further information in respect of special considerations for home and acute haemodialysis The standard together with its constituent parts is directed towards the healthcare professionals involved in the management or routine care of haemodialysis patients and responsible for the quality of dialysis fluid. However, the physician in charge of dialysis has the ultimate responsibility for ensuring that the dialysis fluid is correctly formulated and meets the requirements of all applicable quality standards.

The provisions contained in this document might not be applicable in all circumstances and they are not intended for regulatory application.

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

Part 1:
General requirements

1 Scope

1.1 General

This document is the base standard for a number of other standards dealing with water treatment equipment, water, dialysis water, concentrates, and dialysis fluid (ISO 23500 series) and provides dialysis practitioners with guidance on the preparation of dialysis fluid for haemodialysis and related therapies and substitution fluid for use in online therapies, such as haemodiafiltration and haemofiltration. As such, this document functions as a recommended practice.

This document does not address clinical issues that might be associated with inappropriate usage of the water, dialysis water, concentrates, or dialysis fluid. Healthcare professionals involved in the provision of treatment for kidney failure should make the final decision regarding the applications with which these fluids are used, for example, haemodialysis, haemodiafiltration, high-flux haemodialysis, reprocessing of dialysers, and need to be aware of the issues that the use of inappropriate fluid quality raises in each of the therapies.

The concepts incorporated in this document should not be considered inflexible or static. The recommendations presented here are reviewed periodically by ISO/SC150/TC2/WG5 to address changes in the understanding of the role of dialysis fluid purity in patient outcomes and technological developments.

1.2 Inclusions

This document addresses the user's responsibility for dialysis fluid once the equipment used in its preparation has been delivered and installed.

For the purposes of this document, dialysis fluid includes:

a) dialysis water (see 3.17 for definition) used for the preparation of dialysis fluid and substitution fluid,

b) dialysis water used for the preparation of concentrates at the user's facility,

c) concentrates,

d) the final dialysis fluid and substitution fluid.

The scope of this document includes

a) the quality management of equipment used to treat and distribute water used for the preparation of dialysis fluid and substitution fluid, from the point at which municipal water enters the dialysis facility to the point at which the final dialysis fluid enters the dialyser or the point at which substitution fluid is infused,

b) equipment used to prepare concentrate from powder or other highly concentrated media at a dialysis facility, and

c) preparation of the final dialysis fluid or substitution fluid from dialysis water and concentrates.

NOTE Because water used to prepare dialysis fluid can also be used to reprocess dialysers not marked intended for single use, this aspect of water use is also covered by this document.

1.3 Exclusions

This document does not apply to sorbent-based dialysis fluid regeneration systems that regenerate and recirculate small volumes of dialysis fluid, systems for continuous renal replacement therapy that use pre-packaged solutions, and systems and solutions for peritoneal dialysis.

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 undated references, the latest edition of the referenced document (including any amendments) applies. For dated references, only the edition cited applies.

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

ISO 23500-4, *Preparation and quality management of fluids for haemodialysis and related therapies — Part 4: Concentrates 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*

3 Terms and definitions

For the purposes of this document, the following terms and definitions 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 https://www.electropedia.org/

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

Note 1 to entry: Acetate concentrate can contain glucose.

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

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

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

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

Note 2 to entry: Acid concentrate can contain glucose.

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

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

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

3.5
bicarbonate concentrate
B-concentrate
concentrated preparation of sodium bicarbonate that, when diluted with dialysis water and acid concentrate, makes dialysis fluid used for dialysis

Note 1 to entry: Some bicarbonate concentrates also contain sodium chloride.

Note 2 to entry: Bicarbonate concentrate can be in the form of a liquid or a dry powder.

Note 3 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.

3.6
biofilm
microbially-derived sessile community characterized by cells that are irreversibly attached to a substratum or interface or to each other, are imbedded in a matrix of extracellular polymeric substances that they have produced, and exhibit an altered phenotype with respect to growth rate and gene transcription

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

Note 2 to entry: A certain amount of biofilm formation is considered unavoidable in dialysis water systems. When the level of biofilm is such that the action levels for microorganisms and endotoxins in the dialysis water are routinely reached or exceeded, the operation of the system is compromised from a medical and technical point of view. This level of biofilm formation is often referred to as biofouling.

3.7
bulk delivery
delivery of large containers of concentrate to a dialysis facility

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

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

3.8
central concentrate system
system that prepares and/or stores concentrate at a central point for subsequent distribution to its points of use

3.9
central dialysis fluid delivery system
system that produces dialysis fluid from dialysis water and concentrate or powder at a central point and distributes the dialysis fluid from the central point to individual dialysis machines

3.10
combined chlorine
chlorine that is chemically combined with other compound(s) e.g chlorine and ammonia, a combination that results in the production of chloramine

Note 1 to entry: There is no direct test for measuring combined chlorine, but it can be established indirectly by measuring both total and free chlorine and calculating the difference.

3.11
free chlorine
chlorine present in water as dissolved molecular chlorine (Cl_2), hypochlorous acid (HOCl), and hypochlorite ion (OCl^-)

Note 1 to entry: The three forms of free chlorine exist in equilibrium.

3.12
total chlorine
sum of free and combined chlorine

Note 1 to entry: Chlorine can exist in water as dissolved molecular chlorine, hypochlorous acid, and/or hypochlorite ion (free chlorine) or in chemically combined forms (combined chlorine). Where chloramine is used to disinfect water supplies, chloramine is usually the principal component of combined chlorine.

3.13
colony-forming unit
CFU
aggregation of microorganisms arising from a single cell or multiple cells

[SOURCE: ISO11139:2018,3.53]

3.14
concentrate generator
system where the concentrate is delivered to the user as a powder in a container, suitable for attachment to the dialysis machine with which it is intended to be used, and then the powder is converted into a concentrated solution by the dialysis machine

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

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

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

Note 2 to entry: ISO 23500-5 defines three levels of dialysis fluid in terms of micobiology: standard dialysis fluid, ultrapure dialysis fluid, and online-prepared substitution fluid used for haemodiafiltration.

Note 3 to entry: The dialysis fluid entering the dialyser is referred to as “fresh dialysis fluid”, while the fluid leaving the dialyser is referred to as “spent dialysis fluid”.

Note 4 to entry: Dialysis fluid does not include prepackaged parenteral fluids used in some renal replacement therapies, such as haemodiafiltration and haemofiltration.

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

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

Note 2 to entry: The dialysis fluid delivery system can be an integral part of the dialysis machine or a centralized preparation system which feeds multiple individual dialysis consoles.

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

3.17
dialysis water
water that has been treated to meet the requirements of ISO 23500-3 and which is suitable for use in haemodialysis applications, including the preparation of dialysis fluid, reprocessing of dialysers, preparation of concentrates and preparation of substitution fluid for online convective therapies

3.18
disinfection
process to reduce the number of viable microorgansims to a level specified as appropriate for a defined purpose

[SOURCE: ISO17664:2017 3.3]

3.19
empty-bed contact time
EBCT
time taken by a feed water to pass through an empty volume equal to the volume of a particle bed

Note 1 to entry: EBCT (min) is calculated from the following formula:

$$\text{EBCT} = V/Q$$

where

V is the volume of the particle bed, in cubic metres (m^3);

Q is the flow rate of water through the bed, in cubic metres per minute (m^3/min).

Note 2 to entry: EBCT is used as an indirect measure of how much contact occurs between particles, such as activated carbon, and water as the water flows through a bed of particles.

3.20
endotoxin
lipopolysaccharide component of the cell wall of gram negative bacteria that is heat stable and elicits a variety of inflammatory reponses in humans

[SOURCE: ISO11139:2018,3.101]

Note 1 to entry: [See also *pyrogen* (3.35)].

3.21
endotoxin-retentive filter
ETRF
membrane filter used to remove endotoxins and microorganisms from dialysis water or dialysis fluid

Note 1 to entry: The performance of an endotoxin-retentive filter is usually expressed as the logarithmic reduction value (LRV), defined as $\log_{10}$(inlet concentration)/(outlet concentration).

Note 2 to entry: Endotoxin-retentive filters can be configured in a cross-flow or dead-end mode. Some endotoxin-retentive filters also remove endotoxins by adsorption.

3.22
endotoxin unit
EU
unit assayed by the *Limulus* amoebocyte lysate (LAL) test when testing for endotoxins

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

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

3.23
feed water
water supplied to a water treatment system or to an individual component of a water treatment system

Note 1 to entry: the water supplied to the water treatment system is potable water that meets drinking water requirements.

3.24
germicide
agent that kills microorganisms

3.25
haemodiafiltration
process whereby concentrations of water-soluble substances in a patient's blood and an excess of fluid of a patient are corrected by a simultaneous combination of HD and HF

[SOURCE: IEC 60601-2-16:2018, 201.3.208]

3.26
haemodialysis
process whereby concentrations of water-soluble substances in a patient's blood and an excess of fluid of a patient are corrected by bidirectional diffusive transport and ultrafiltration across a semi-permeable membrane separating the blood from the dialysis fluid

[SOURCE: IEC 60601-2-16:2018, 201.3.209]

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

3.27
haemofiltration
process whereby concentrations of water-soluble substances in a patient's blood and an excess of fluid of a patient are corrected by convective transport via ultrafiltration and partial replacement by a substitution fluid resulting in the required net fluid removal

[SOURCE: IEC 60601-2-16:2018, 201.3.211]

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

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

3.28
heterotrophic
not self-sustaining, i.e. a type of nutrition in which organisms derive energy from the oxidation of organic compounds by either consumption or absorption of other organisms

3.29
initial validation.
Complete validation (IQ, OQ, PQ1 + PQ2) of the entire water treatment system. Initial validation is performed on new systems, completely unknown systems or a system following major repairs, where new and previous version of system are not comparable (values of validations are not comparable). In systems without major changes Initial Validation is performed only once in lifetime of a system. Initial Validation is subdivided into: Prospective Initial Validation andConcurrent Initial Validation

3.30
LAL test
***Limulus* amoebocyte lysate test**
assay used to detect endotoxin

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

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

3.31
manufacturer
entity that designs, makes, fabricates, assembles, or processes a particular item or object.

Note 1 to entry: Manufacturer includes, but is not limited to, those who perform the functions of contract sterilization, installation, relabelling, remanufacturing, repacking, or specification development, and initial distributions of foreign entities performing these functions.

Note 2 to entry: Manufacturer does not cover the preparation of concentrates from pre-packaged dry chemicals at a dialysis facility or the handling of bulk concentrates at a dialysis facility as responsibility for the concentrate is transferred from the manufacturer to the user.

3.32
microbiological contamination
presence of unintended bacteria, fungi,protozoa or viruses

[SOURCE: ISO11139:2018.3.171]

3.33
non-pyrogenic
not eliciting a pyrogen reaction

Note 1 to entry: This definition is applicable for fluids produced by online techniques, e.g. substitution and priming fluids.