FINAL DRAFT
International Standard

ISO/FDIS 23500-1

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

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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 23500-1:2019), which has been technically revised.

The main changes are as follows:

— the use of WHO Drinking Water Guideline as the main drinking water quality reference instead of the US EPA or other European standards,

— the removal of thallium from the list of contaminants, as no studies have reported data to indicate that this contaminant is of particular concern in the haemodialysis setting.

— the inclusion of alternative water treatment technologies (e.g. reverse osmosis pre-treatment with ultrafiltration) in the section dealing with water treatment technology

— the addition of a new annex (Annex H), to provide clarification of the different water quality monitoring approaches (online versus offline monitoring);

— the microbiological analytic methods have been updated to include endotoxin testing using recombinant Factor C (tp), flow cytometry, autofluorescence and rapid tests (e.g. ATP);

— the addition of a new annex (Annex I) to provide guidance on risk assessment;

— the validation of water treatment systems has been revised to include validation steps e.g. installation qualification, operational qualification, performance qualification and revalidation);

— further guidance has been added on technical needs after typical technical interventions in Clause 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 standards dealing with water treatment and the production of dialysis fluid in the 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 in this document, the user is advised to follow the manufacturer's instructions regarding the operation and maintenance of equipment. In 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 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 can be required and how it should be configured; the descriptions are not intended to be 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 do 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 can be found in improperly prepared dialysis fluid. Annexes F and G provide further information in respect of special considerations for home and acute haemodialysis. This document 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.

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

Part 1:
General requirements

1 Scope

This document specifies the general requirements for the preparation of fluids for haemodialysis and related therapies and substitution fluid for use in online therapies, such as haemodiafiltration and haemofiltration, for dialysis practitioners. This document gives guidance on the user's responsibility for fluids used in haemodialysis and related therapies once the equipment used in its preparation has been delivered and installed. 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.

This document is applicable to

— 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.

— the quality management of the equipment used to prepare acid and bicarbonate concentrate from powdered or other highly concentrated media at a dialysis facility, and

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

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,

— systems and solutions for peritoneal dialysis.

This document does not address clinical issues associated with inappropriate usage of such fluids.

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 23500-2, *Preparation and quality management of fluids for haemodialysis and related therapies — Part 2: Water treatment equipment for haemodialysis applications and related therapies*

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 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
acetate concentrate
concentrated solution of salts containing acetate, which when diluted with *dialysis water* (3.17), yields bicarbonate-free *dialysis fluid* (3.15) 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
low pH mixture of salts that, when diluted with *dialysis water* (3.17) and *bicarbonate concentrate* (3.6), yields *dialysis fluid* (3.15) for use in dialysis

Note 1 to entry: The term “acid” refers to the small amount of acid (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
value from monitoring that necessitates immediate intervention

[SOURCE: ISO 13408-1:2023, 3.1, modified — the word particulate has been excluded.]

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 its packaging

3.5
bacteria and endotoxin-retentive filter
BERF
endotoxin retentive filter
ERTF
membrane filter used to remove *endotoxins* (3.20) and microorganisms from *dialysis water* (3.17) or *dialysis fluid* (3.15)

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

3.6
bicarbonate concentrate
B-concentrate
concentrated preparation of sodium bicarbonate that, when diluted with *dialysis water* (3.17) and *acid concentrate* (3.2), makes *dialysis fluid* (3.15) 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.

3.7
biofilm
microbially-derived sessile community characterized by cells that are irreversibly attached to a substratum or interface or to each other, are embedded 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* (3.17) systems. When the level of biofilm is such that the *action levels* (3.3) for microorganisms and *endotoxins* (3.20) 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.

3.8
bulk delivery
delivery of large containers of concentrate to a dialysis facility

Note 1 to entry: Bulk delivery canbe containers such as drums, which can be pumped into a *storage tank* (3.41) maintained at the *user*'s (3.44) 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.

3.9
central concentrate system
system that prepares and/or stores concentrate at a central point for subsequent distribution to its points of use

3.10
central dialysis fluid delivery system
system that produces *dialysis fluid* (3.15) from *dialysis water* (3.17) and concentrate or powder at a central point and distributes the dialysis fluid from the central point to individual dialysis machines

3.11
combined chlorine
chlorine that is chemically combined with other compound(s), such as ammonia, and 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* (3.12) and calculating the difference.

3.12
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.

3.13
total chlorine
sum of *free chlorine* (3.12) and *combined chlorine* (3.11)

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.

3.14
colony-forming unit
CFU
aggregation of microorganisms arising from a single cell or multiple cells

[SOURCE: ISO 11139:2018, 3.53, modified — "visible" has been deleted at the beginning of the definition.]

3.15
dialysis fluid
DEPRECATED: dialysate
DEPRECATED: dialysis solution
Note 1 to entry: aqueous fluid made from *dialysis water* (3.17) containing electrolytes and, usually, buffer and glucose, that is delivered to the dialyser by the *dialysis fluid delivery system* (3.16), which is intended to exchange solutes with blood during *haemodialysis* (3.24) and *haemodiafiltration* (3.23)

Note 2 to entry: ISO 23500-5 defines three levels of dialysis fluid in terms of microbiology: standard dialysis fluid, ultrapure dialysis fluid and online-prepared *substitution fluid* (3.42) 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 pre-packaged parenteral fluids used in some renal replacement therapies, such as haemodiafiltration and *haemofiltration* (3.25).

3.16
dialysis fluid delivery system
device that

— prepares *dialysis fluid* (3.15) online from *dialysis water* (3.17) 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* (3.18) 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 dialysis fluid delivery systems.

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* (3.34) 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* (3.24) applications, including the preparation of *dialysis fluid* (3.15), reprocessing of dialysers, preparation of concentrates and preparation of *substitution fluid* (3.42) for online convective therapies

Note 1 to entry: Some integrated, validated systems, and other new systems by alternative design can provide ultrapure dialysis water with <0,1 CFU/ml and <0,03 EU/ml. By mixing with *sterile* (3.40) and *non-pyrogenic* (3.31) concentrates and by utilising sterile and non-pyrogenic dialysis fluid pathway, ultrapure dialysis fluid can be produced in such integrated and validated systems**.**

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

3.19
empty-bed contact time
EBCT
measure of the time during which water to be treated is in contact with the treatment medium in a contact vessel, assuming that all liquid passes through the vessel at the same velocity

Note 1 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.

Note 2 to entry: EBCT, expressed in minutes, is calculated from:

$$t_{EBCT} = v/q$$

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).

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

Note 1 to entry: [see also *pyrogen* (3.36)].

[SOURCE: ISO 11139:2018, 3.101, modified — "animals and" has been deleted from the definition and Note 1 to entry has been added.]

3.21
endotoxin unit
EU
unit assayed by the *Limulus* amoebocyte lysate (LAL) test when testing for *endotoxins* (3.20)

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.

3.22
germicide
agent that kills microorganisms

3.23
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]

3.24
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* (3.15)

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.

[SOURCE: IEC 60601-2-16:2018, 201.3.209, modified — Note 1 to entry has been added.]

3.25
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* (3.42) resulting in the required net fluid removal

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* (3.25)] 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* (3.15) stream in haemofiltration.

[SOURCE: IEC 60601-2-16:2018, 201.3.211, modified — Notes 1 and 2 to entry have been added.]

3.26
heterotrophic
organism that cannot produce its own food, instead taking nutrition from other sources of organic compounds for metabolic synthesis

3.27
initial validation
installation qualification
IQ
complete *validation* (3.45) of the entire *water treatment system* (3.48) or *dialysis fluid* (3.15) preparation systems following installation

Note 1 to entry: 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 and concurrent initial validation.

3.28
***Limulus* amoebocyte lysate test**
LAL test
test for measuring bacterial *endotoxins* (3.20) using *Limulus* amebocyte lysate reagent

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 endotoxins.