INTERNATIONAL STANDARD

ISO 23500

First edition
2011-05-15

Guidance for the preparation and quality management of fluids for haemodialysis and related therapies

Directives concernant la préparation et le management de la qualité des fluides d'hémodialyse et de thérapies annexes

Reference number
ISO 23500:2011(E)

ISO copyright office
Case postale 56 • CH-1211 Geneva 20
Tel. + 41 22 749 01 11
Fax + 41 22 749 09 47
E-mail copyright@iso.org
Web www.iso.org

Published in Switzerland

Contents

Page

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.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

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.

ISO 23500 was prepared by Technical Committee ISO/TC 150, *Implants for surgery*, Subcommittee SC 2, *Cardiovascular implants and extracorporeal systems*.

Introduction

This International Standard was developed by Working Group 5 of ISO/TC 150/SC 2. The Working Group's objective was to provide users with guidance for handling water and concentrates and for the production and monitoring 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.

Quality requirements for the water and concentrates used to prepare dialysis fluid, and for that dialysis fluid, are provided in ISO 13959, ISO 13958 and ISO 11663, respectively. This International Standard does not address clinical issues that might be associated with inappropriate usage of the water, concentrates or final 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, and the 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 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 International Standard provides guidance on monitoring 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 provides a general description of the system components that are used for water treatment and concentrate 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 26722.

The verbal forms used in this International Standard conform to usage described in Annex H of the ISO/IEC Directives, Part 2:2004. For the purposes of this standard, the auxiliary verb:

— "shall" means that compliance with a requirement or a test is mandatory for compliance with this standard;

— "should" means that compliance with a requirement or a test is recommended but is not mandatory for compliance with this standard;

— "may" is used to describe a permissible way to achieve compliance with a requirement or test.

This International Standard 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 monitoring of dialysis fluid for haemodialysis. This International Standard is directed towards the healthcare professionals involved in the management of haemodialysis patients and healthcare professionals involved in the routine care of haemodialysis patients. The recommendations contained in this International Standard might not be applicable in all circumstances and they are not intended for regulatory application.

The guidance provided by this International Standard should help protect haemodialysis patients from adverse effects arising from known chemical and microbial contaminants that might be found in improperly prepared 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 concepts incorporated in this International Standard should not be considered inflexible or static. The recommendations presented here should be reviewed periodically in order to assimilate increased understanding of the role of dialysis fluid purity in patient outcomes and technological developments.

Guidance for the preparation and quality management of fluids for haemodialysis and related therapies

1 Scope

1.1 General

This International Standard 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 International Standard functions as a recommended practice.

1.2 Inclusions

This International Standard addresses the user's responsibility for the dialysis fluid once the equipment used in its preparation has been delivered and installed. For the purposes of this International Standard, the dialysis fluid includes water used for the preparation of dialysis fluid and substitution fluid, water used for the preparation of concentrates at the user's facility, as well as concentrates and the final dialysis fluid and substitution fluid.

Included in the scope of this International Standard are

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 is commonly prepared and distributed using the same equipment as the water used to reprocess dialysers, water used to reprocess dialysers is also covered by this International Standard.

1.3 Exclusions

Excluded from the scope of this International Standard are sorbent-based dialysis fluid regeneration systems that regenerate and recirculate small volumes of dialysis fluid, systems for continuous renal replacement therapy that use prepackaged solutions, and systems and solutions for peritoneal dialysis.

2 Normative references

The following referenced documents are indispensable for the application 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 13958:2009, *Concentrates for haemodialysis and related therapies*

ISO 13959:2009, *Water for haemodialysis and related therapies*

ISO 11663:2009, *Quality of dialysis fluid for haemodialysis and related therapies*

ISO 26722:2009, *Water treatment equipment for haemodialysis applications and related therapies*

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

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 Acetate concentrate may contain glucose.

NOTE 2 Acetate is used to provide buffer in place of sodium bicarbonate.

NOTE 3 Acetate concentrate is used as a single concentrate.

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

NOTE 1 The term “acid” refers to the small amount of acid (usually acetic acid) that is included in the concentrate.

NOTE 2 Acid concentrate may contain glucose.

NOTE 3 Acid concentrate may 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 Sodium bicarbonate is also known as sodium hydrogen carbonate.

NOTE 2 Some bicarbonate concentrates also contain sodium chloride.

NOTE 3 Bicarbonate concentrate may be in the form of a liquid or a dry powder.

NOTE 4 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 The matrix, a slimy material secreted by the cells, protects the bacteria from antibiotics and chemical disinfectants.

NOTE 2 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 cannot be routinely achieved, 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
bleach
solution of sodium hypochlorite normally used for household cleaning and disinfection

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

NOTE 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.

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 from dialysis water and concentrate or powder at a central point and distributes the dialysis fluid from the central point to individual dialysis machines

3.11
chlorine, combined
chlorine that is chemically combined, such as in chloramine compounds

NOTE There is no direct test for measuring combined chlorine, but it can be measured indirectly by measuring both total and free chlorine and calculating the difference.

3.12
chlorine, free
chlorine present in water as dissolved molecular chlorine (Cl_2), hypochlorous acid (HOCl) and hypochlorite ion (OCl^-)

NOTE The three forms of free chlorine exist in equilibrium.

3.13
chlorine, total
sum of free and combined chlorine

NOTE 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
measure of bacterial or fungal cell numbers that theoretically arise from a single cell when grown on solid media

NOTE Colonies can also form from groups of organisms when they occur in aggregates.

3.15
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 The solution produced by the concentrate generator is used by the dialysis machine to make the final dialysis fluid delivered to the dialyser.

3.16
dialysis fluid
dialysate
dialysis solution
aqueous fluid containing electrolytes and, usually, buffer and glucose, which is intended to exchange solutes with blood during haemodialysis

NOTE 1 The term “dialysis fluid” is used throughout this International Standard 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” may be used in place of dialysis fluid.

NOTE 2 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 3 Dialysis fluid does not include prepackaged parenteral fluids used in some renal replacement therapies, such as haemodiafiltration and haemofiltration.

3.17
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 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 The dialysis fluid delivery system may be an integral part of the single-patient dialysis machine or a centralized preparation system which feeds multiple bedside monitoring systems.

NOTE 3 Dialysis fluid delivery systems are also known as proportioning systems and dialysis fluid supply systems.

3.18
dialysis water
water that has been treated to meet the requirements of ISO 13959 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

3.19
disinfection
destruction of pathogenic and other kinds of microorganisms by thermal or chemical means

NOTE Disinfection is a less lethal process than sterilization, because it destroys most recognized pathogenic microorganisms but does not necessarily destroy all microbial forms.

3.20
empty-bed contact time
EBCT
time taken by a fluid to pass through an empty volume equal to the volume of a particle bed

NOTE 1 EBCT (min) is calculated from the following equation:

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

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 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.

3.21
endotoxin
major component of the outer cell wall of gram-negative bacteria

NOTE Endotoxins are lipopolysaccharides, which consist of a polysaccharide chain covalently bound to lipid A. Endotoxins can acutely activate both humoral and cellular host defences, leading to a syndrome characterized by fever, shaking, chills, hypotension, multiple organ failure, and even death if allowed to enter the circulation in a sufficient dose [see also **pyrogen** (3.37)].

3.22
endotoxin-retentive filter
ETRF
membrane filter used to remove endotoxins and microorganisms from dialysis water or dialysis fluid

NOTE 1 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 Endotoxin-retentive filters may be configured in a cross-flow or dead-end mode. Some endotoxin-retentive filters also remove endotoxins by adsorption.

3.23
endotoxin units
EU
units assayed by the *Limulus* amoebocyte lysate (LAL) test when testing for endotoxins

NOTE 1 Because activity of endotoxins depends on the bacteria from which they are derived, their activity is referred to a standard endotoxin.

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

3.24
feed water
water supplied to a water treatment system or an individual component of a water treatment system

3.25
germicide
agent that kills microorganisms

3.26
haemodiafiltration
form of renal replacement therapy in which waste solutes are removed from blood by a combination of diffusion and convection through a high-flux membrane

NOTE Diffusive solute removal is achieved using a dialysis fluid stream as in haemodialysis. Convective solute removal is achieved by adding ultrafiltration in excess of that needed to obtain the desired weight loss; fluid balance is maintained by infusing a replacement solution into the blood either before the dialyser (predilution haemodiafiltration), after the dialyser (postdilution haemodiafiltration), or a combination of the two (mixed dilution haemodiafiltration).

3.27
haemodialysis
form of renal replacement therapy in which waste solutes are removed primarily by diffusion from blood flowing on one side of a membrane into dialysis fluid flowing on the other side

NOTE Fluid removal that is sufficient to obtain the desired weight loss is achieved by establishing a hydrostatic pressure gradient across the membrane. This fluid removal provides some additional waste solute removal, particularly for solutes with higher molecular weight.

3.28
haemofiltration
form of renal replacement therapy in which waste solutes are removed from blood by convection

NOTE 1 Convective transport is achieved by ultrafiltration through a high-flux membrane. Fluid balance is maintained by infusing a replacement solution into the blood either before the haemofilter (predilution haemofiltration), after the haemofilter (post-dilution haemofiltration), or a combination of the two (mixed dilution haemofiltration).

NOTE 2 There is no dialysis fluid stream in haemofiltration.

3.29
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

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

NOTE The detection method uses the chemical response of an extract from blood cells of the horseshoe crab (*Limulus polyphemus*) to endotoxins.

3.31
manufacturer
entity that designs, manufactures, fabricates, assembles or processes a finished device

NOTE Manufacturers include, but are 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. The term does not cover preparation of concentrates from prepackaged dry chemicals at a dialysis facility or the handling of bulk concentrates at a dialysis facility after responsibility for the concentrate is transferred from the manufacturer to the user.

3.32
microbiological contamination
contamination with any form of microorganism (e.g. bacteria, yeast, fungi and algae) or with the by-products of living or dead organisms, such as endotoxins, exotoxins and cyanobacterial toxins (derived from blue-green algae)

3.33
microfilter
filter designed to remove particles larger than 0,1 µm in size

NOTE Microfilters have an absolute size cut-off and are available in both dead-end and cross-flow configurations. Some microfilters can reduce the concentration of endotoxins by a process of adsorption.

3.34
nonpyrogenic
having less than 0,03 EU/ml

NOTE Historically, the threshold pyrogenic dose of 5 EU/kg/h (the minimum dose that produces fever) has been used to set endotoxin limits of devices and injectable medications.

3.35
product water
water produced by a water treatment system or by an individual device thereof

3.36
proportioning system
apparatus that proportions dialysis water and haemodialysis concentrate to prepare dialysis fluid

3.37
pyrogen
fever-producing substance

NOTE Pyrogens are most often lipopolysaccharides of gram-negative bacterial origin (see also **endotoxin**).

3.38
sterile
free from viable microorganisms

NOTE 1 “Sterile” can be used to describe a packaged solution that was prepared using a terminal sterilization process validated according to the methods of the applicable pharmacopoeia. A terminal sterilization process is commonly defined as one that achieves a sterility assurance level (SAL) of 10^{-6}, i.e. assurance of less than one chance in a million that viable microorganisms are present in the sterilized article.

NOTE 2 Alternatively, “sterile” can be used to describe a solution prepared for immediate use by a continuous process, such as filtration, that has been validated according to the methods of the applicable pharmacopoeia to produce a solution free of microorganisms for the validated life of the filter.

3.39
storage tank
tank at the user's facility for storage of dialysis water or concentrate from bulk deliveries, or for concentrate prepared in bulk at the user's facility from powder and dialysis water

3.40
substitution fluid
fluid used in haemofiltration and haemodiafiltration treatments which is infused directly into the patient's blood as a replacement for the fluid that is removed from the blood by filtration

NOTE 1 Substitution fluid is also referred to as substitution solution or replacement solution.

NOTE 2 Substitution fluid may also be used for bolus administration, for priming of an extracorporeal blood circuit and for returning blood to the patient at the end of a treatment.

3.41
total dissolved solids
TDS
sum of all ions in a solution, often approximated by means of electrical conductivity or resistivity measurements

NOTE TDS measurements are commonly used to assess the performance of reverse osmosis units. TDS values are often expressed in terms of $CaCO_3$, NaCl, KCl, or 442 equivalents, in milligrams per litre (mg/l). [442 is a solution of sodium sulfate (40 %), sodium bicarbonate (40 %), and sodium chloride (20 %) that closely represents the conductivity to concentration relationship, on average, for naturally occurring fresh water.]

3.42
ultrapure dialysis fluid
highly purified dialysis fluid that can be used in place of conventional dialysis fluid

NOTE A widely accepted specification of ultrapure dialysis fluid is <0,1 CFU/ml and <0,03 EU/ml.

3.43
user
physician or physician's representative responsible for the actual production and handling of dialysis fluid

NOTE This International Standard is directed to the “user”.

3.44
validation
process of documenting that the water treatment and dialysis fluid production systems, when installed and operated according to the manufacturer's recommendations, consistently produce water or dialysis fluid meeting the stipulated quality levels

NOTE 1 In this context, validation also includes demonstrating that the system is “fit for purpose”.

NOTE 2 The term “verification” is also used and refers to demonstrating that the system complies with applicable regulations, specifications, or other conditions. A dialysis facility might be interested in both validation and verification of its fluid production systems.

3.45
water treatment system
collection of water treatment devices and associated piping, pumps, valves, gauges, etc., that together produce water for dialysis meeting the requirements of ISO 13959 for haemodialysis applications and deliver it to the point of use

4 Summary of quality requirements of ISO 13958, ISO 13959 and ISO 11663

The quality requirements set forth in this clause are reproduced from the 2009 editions of ISO 13958, ISO 13959 and ISO 11663. The latest editions of these International Standards should be consulted to ascertain if there have been any changes to those requirements before implementing the recommendations of this International Standard.

4.1 Dialysis water

4.1.1 General

The requirements contained in this clause apply to dialysis water at its point of use. As such, these requirements apply to the water treatment system as a whole and not to each of the devices that make up the system. However, collectively, the individual devices shall produce water that, at a minimum, meets the requirements of this clause.

4.1.2 Chemical contaminants in dialysis water

Dialysis water shall not contain substances at levels greater than those listed in ISO 13959 (see Tables 1 and 2). The manufacturer or supplier of a complete water treatment system should recommend a system that is capable of meeting these requirements based on a feed-water analysis. The system design should reflect possible seasonal variations in feed-water quality. The manufacturer or supplier of a complete water treatment and distribution system should demonstrate that the complete water treatment, storage and distribution system is capable of meeting the requirements of ISO 13959 at the time of installation.

Following installation of a water treatment, storage and distribution system, the user is responsible for regular monitoring of the levels of chemical contaminants in the water and for complying with the requirements of this International Standard.

Tables 1 and 2 are reproduced from ISO 13959:2009.