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Fluids for haemodialysis and related therapies

Fluides d'hémodialyse et de thérapies annexes

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Foreword

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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 Subcommittee SC 2, Cardiovascular implants and extracorporeal systems.

Introduction

This International Standard was developed by the Technical Committee of ISO/TC 150/SC 2 WG5. The Working Group's objective is to provide rational guidelines for handling water and concentrates and for the production and monitoring of dialysate used for haemodialysis. The need for such guidelines is based on the critical role of dialysate quality in providing safe and effective haemodialysis, and the recognition that day-to-day dialysate quality is under the control of the health care professionals who deliver dialysis therapy.

This International Standard reflects the conscientious efforts of health care professionals, patients, and medical device manufacturers to develop recommendations for handling water and concentrates and for the production and monitoring of dialysate for haemodialysis. This international standard is directed towards the healthcare professionals involved in the management of dialysis facilities and healthcare professionals involved in the routine care of patients treated in dialysis facilities.The recommendations contained in this document may not be applicable in all circumstances and they are not intended for regulatory application.

The use to which the water is put is not within the control of the equipment or equipment provider, thus, this standard cannot address the clinical issues that may be associated with inappropriate usage of the product water and the final dialysate. Healthcare professionals involved in the provision of treatment for renal failure must make the final decision regarding the applications with which the water provided is used for, e.g. haemodialysis, haemodiafiltration, high flux dialysis, and the reprocessing of dyalisers, and need to be aware of the issues that the use of inappropriate water quality raises in each of the therapies.

The equipment used in the various stages of dialysate preparation is generally obtained from specialized vendors. This International Standard provides a general description of the system components that these vendors may provide. These descriptions are intended to provide the user with a basis for understanding why certain equipment may be required and how it should be configured; they are not intended as detailed design standards. Dialysis practitioners are generally responsible for maintaining the equipment used to prepare dialysate following its installation. Therefore, this International Standard provides guidance on monitoring and maintenance of the equipment to ensure that dialysate 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.

The guidance provided by this International Standard should help protect haemodialysis patients from adverse effects arising from known chemical and microbial contaminants that may be found in improperly prepared dialysate. However, the physician in charge of dialysis has the ultimate responsibility for ensuring that the dialysate 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 dialysate purity in patient outcomes and technological developments.

Fluids for haemodialysis and related therapies

1 Scope

1.1 General

The intent of this International Standard is to provide dialysis practitioners with guidance on the preparation of dialysate for haemodialysis and related therapies, from the point at which municipal water enters their dialysis facility to the point at which the final dialysate enters the dyaliser, and as such functions as a recommended practice. Included in the scope of the International Standard are: (1) use, maintenance, and monitoring of equipment used to purify and distribute water used for the preparation of dialysate and other haemodialysis applications; (2) use, maintenance, and monitoring of equipment used to prepare concentrate from powder at a dialysis facility; and (3) preparation of the final dialysate from purified water and concentrate.

1.2 Inclusions

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

NOTE Because water used to prepare dialysate is commonly prepared and distributed using the same equipment as the water used reprocess dyalisers, water used to reprocess dyalisers is also covered by this International Standard.

1.3 Exclusions

Excluded from the scope of this International Standard are sorbent-based dialysate regeneration systems that regenerate and recirculate small volumes of dialysate, 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 13959, *Water for haemodialysis and related therapies*

ISO 13958, *Concentrates for haemodialysis and related therapies*

3 Definitions

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

3.1
acetate concentrate
concentrated solution of salts that may contain glucose, which, when diluted with water, yields dialysate for use in dialysis. Sodium acetate is normally used as the buffer

NOTE 1 This concentrate is used as a single concentrate.

NOTE 2 In some cases glucose is also known as dextrose.

3.2
acetate dialysate
dialysate without bicarbonate, using acetate as a substitute for the bicarbonate buffer

NOTE Acetate dialyzing fluid is generally produced from a single concentrate. Acetate is metabolized by the patient to produce bicarbonate.

3.3
acid concentrate
acidified concentrated solution of salts that may contain glucose, which, when diluted with water and bicarbonate concentrate, yields dialysate for use in dialysis

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

3.4
action level
concentration of a contaminant at which steps should be taken to interrupt the trend toward higher, unacceptable levels

3.5
anions
ions carrying a negative charge

3.6
available chlorine
free ClO- ions, dissolved molecular chlorine

3.7
bacteriology
area of study within the field of microbiology that deals with the study of bacteria

3.8
batch system
apparatus in which the dialysate is prepared in bulk before each dialysis session

3.9
bicarbonate concentrate
concentrated solution of sodium bicarbonate that, when diluted with water and acid concentrate, makes dialysate used for dialysis

NOTE 1 Some bicarbonate concentrates also contain sodium chloride.

NOTE 2 Bicarbonate is also known as Sodium hydrogen carbonate.

3.10
bicarbonate dialysate
dialysate containing physiological or higher concentrations of bicarbonate

NOTE Bicarbonate dialysate is generally produced from two concentrates: one containing bicarbonate and the other containing acid and other electrolytes (see **acid concentrate** and **bicarbonate concentrate**).

3.11
bleach
a solution of sodium hypochlorite normally used for household cleaning and disinfection

3.12
biofilm
coating on surfaces that consists of microcolonies of bacteria embedded in a protective extracellular matrix. The matrix, a slimy material secreted by the cells, protects the bacteria from antibiotics and chemical disinfectants

3.13
bulk delivery
delivery of large volumes of concentrate in which the product is transferred (pumped) from the delivery container to a user's storage tank

3.14
cations
ions carrying a positive charge

3.15
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.

3.16
chlorine, free
dissolved molecular chlorine

3.17
colony-forming unit (CFU)
organism capable of replicating to form a distinct, visible colony on a culture plate. In practice, a colony may be formed by a group of organisms

3.18
concentrate generators
system in which the concentrate is delivered to the consumer as a powder in a container and then converted online into a saturated solution by a dialysis delivery machine

NOTE This solution is used by an individual proportioning system to make the final dialysate delivered to the dyaliser.

3.19
dialysate
aqueous fluid containing electrolytes and, usually, glucose, which is intended to exchange solutes with blood during haemodialysis

NOTE The word "dialysate" is used throughout this document to mean the fluid made from water and concentrates that is delivered to the dyaliser by the dialysate supply system. Such phrases as "dialysis fluid," "dialyzing fluid" or "dialysis solution" may be used in place of dialysate.

3.20
central dialysate delivery systems (CDS)
dialysate systems that produce dialysate at a central point and distribute the prepared dialysate to the dialysis control station

3.21
dialysate supply system
devices that: (1) prepare dialysate online from water and concentrates or that store and distribute premixed dialysate; (2) circulate the dialysate through the dyaliser; (3) monitor the dialysate for temperature, conductivity (or equivalent), pressure, flow, and blood leaks; and (4) prevent dialysis during disinfection or cleaning modes

NOTE 1 The dialysate supply system includes reservoirs, conduits, proportioning devices for the dialysate, and monitors and associated alarms and controls assembled as a system for the characteristics listed above.

NOTE 2 The dialysate supply system may be an integral part of the single patient dialysis machine or a centralized preparation system which feeds multiple bedside monitoring systems.

3.22
disinfection
destruction of pathogenic and other kinds of microorganisms by thermal or chemical means

NOTE 1 Disinfection is a less lethal process than sterilization, because it destroys most recognized pathogenic microorganisms but does not necessarily destroy all microbial forms.

NOTE 2 This definition of "disinfection" is equivalent to low-level disinfection in the Spalding classification.

3.23
electrolyte
ion capable of transferring or exchanging electrons

NOTE In dialysate, the electrolytes are the charged ions that result from dissociation of salts when they are dissolved in water. These charged ions are responsible for the conductive property of dialysate.

3.24
empty-bed contact time (EBCT)
measure of how much contact occurs between particles, such as activated carbon, and water as the water flows through a bed of the particles

NOTE

EBCT (min) is calculated from the following equation:

$$EBCT = V/Q$$

where

V is the volume of particles in the bed (meter^3);

Q is the flow rate of water through the bed (meter^3/min).

3.25
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 defenses, 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**)

3.26
endotoxin units (EU)
units assayed by the *Limulus* amoebocyte lysate (LAL) method when testing for endotoxins

NOTE 1 Because activity of endotoxins differs on a mass basis, their reference to a standard *E. coli* endotoxin has been established and is used to compare various lots of product.

NOTE 2 In some countries, endotoxin concentrations are expressed in international units (IU). Since the 1983 harmonization of endotoxin assays, EU and IU are equivalent.

3.27
feed water
water supplied to a water treatment system or an individual component of the system

3.28
germicide
agent that kills microorganisms

3.29
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 dialysate 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 dyaliser (predilution haemodiafiltration) or after the dyaliser (postdilution haemodiafiltration).

3.30
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 dialysate 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 higher molecular weight solutes.

3.31
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 (pre-dilution haemofiltration) or after the haemofilter (post-dilution haemofiltration).

NOTE 2 There is no dialysate stream in haemofiltration.

3.32
heterotrophic
not self-sustaining; a type of nutrition in which organisms derive energy from the oxidation of organic compounds either by consumption or absorption of other organisms

3.33
***Limulus* amoebocyte lysate (LAL) test**
assay used to detect endotoxin

NOTE The detection method uses the chemical specific response of the horseshoe crab (Limulus polyphemus) to endotoxin.

3.34
manufacturer
person who 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, relabeling, remanufacturing, repacking, or specification development, and initial distributions of foreign entities performing these functions.

3.35
microbial
referring to microscopic organisms, bacteria, fungi, and so forth (see also **bacteriology**)

3.36
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 microcystin (derived from blue-green algae)

3.37
microfilter
filter designed to remove particles in the range 0,1 µm to 3 µm in diameter

NOTE Microfilters have an absolute size cut-off and are available in both dead-end and cross-flow configurations.

3.38
product water
water produced by a water treatment system or by an individual component of a system

3.39
proportioning system
apparatus that proportions water and haemodialysis concentrate to prepare dialysate

3.40
pyrogen
fever-producing substance. Note that pyrogens are most often lipopolysaccharides of gram-negative bacterial origin (see also **endotoxin**)

3.41
spike
small amount of a single chemical used to increase a constituent or constituents in the concentrate for a single patient's treatment

NOTE The spike may be in the form of a dry chemical or may be dissolved in water.

3.42
sterile
free from viable microorganisims

NOTE For solutions used in haemodialysis and related therapies, "sterile" can be used to describe a packaged solution that was prepared using a terminal sterilization process that has been demonstrated to achieve a probability of 10^{-6} that only one appropriate indicator microorganism can survive. Alternatively, "sterile" can be used to describe a solution prepared for immediate use by a continuous filtration process that has been validated to produce a solution free of microorganisms even if one filtration step fails.

3.43
storage tank
large tank at the user's facility for storage of purified water or concentrate from bulk deliveries, or for concentrate prepared in bulk at the user's facility from powder and purified water

3.44
substitution fluid
fluid used in hemofiltration and hemodiafiltration treatments that is infused directly into the patient's blood as a replacement for the fluid that is removed from the blood by filtration

NOTE Substitution fluid may also be refered to as substitution solution or replacement solution.

3.45
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 $CaCO_3$ or NaCl equivalents (ppm).

3.46
ultrafilter
membrane filter with a pore size in the range 0,001 µm to 0,05 µm

NOTE Performance is usually rated in terms of a nominal molecular weight cut-off (MWCO), which is defined as the smallest molecular weight species for which the filter membrane has more than 90 % rejection. Depending on their nominal MWCO, ultrafilters may be used to remove particles and solutes as small as 1 000 dalton.

NOTE Ultrafilters may be configured in a cross-flow or dead ended mode. Some ultrafilters also remove endotoxins by adsorption.

3.47
ultrapure dialysate
highly purified dialysate that can be used in place of conventional dialysate or as feed solution for further processing to create fluid intended for injection directly into the blood

NOTE The definition of “ultrapure dialysate” varies, but the recommendation used in the European Renal Association–European Dialysis and Transplant Association (ERA/EDTA) Best Practice Guidelines (ERA–EDTA, 2002) is < 0.1 CFU/mL and < 0.03 EU/mL.

3.48
user
physician or physician’s representative responsible for the actual production and handling of dialysate

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

3.49
water treatment system
collection of water purification devices and associated piping, pumps, valves, gauges, etc., that together produce purified water for haemodialysis applications and deliver it to the point of use

4 Requirements

4.1 Water

4.1.1 General

The requirements contained in Clause 4.1 apply to the purified water as it enters the equipment used to prepare dialysate or concentrates from powder at a dialysis facility. 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 Requirements for chemical contaminants in water

Product water used to prepare dialysate or concentrates from powder at a dialysis facility, or to process dyalisers for reuse, shall not contain chemical contaminants at concentrations in excess of those listed in Table 1 below. The manufacturer or supplier of a complete water treatment system should recommend a system that is capable of meeting the requirements of this clause given the analysis of the feed water. The system design should reflect possible seasonal variations in feed water quality. The manufacturer or supplier of a complete water treatment and distribution system shall 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 continued monitoring of the levels of chemical contaminants in the water and for complying with the requirements of this standard.

Table 1—Maximum allowable chemical contaminant levels in water used to prepare dialysate and concentrates from powder at a dialysis facility and to reprocess dyalisers for multiple uses

	Contaminant	Maximum Concentration (mg/L)[b)]
Contaminants with documented toxicity in hemodialysis		
	Aluminum	0,01
	Chloramines	0,1
	Free chlorine	0,5

	Contaminant	Maximum Concentration (mg/L)[b]
	Copper	0,1
	Fluoride	0,2
	Lead	0,005
	Nitrate (as N)	2
	Sulfate	100
	Zinc	0,1
Contaminants normally included in dialysate		
	Calcium	2 (0,1 mEq/L)
	Magnesium	4 (0,3 mEq/L)
	Potassium	8 (0,2 mEq/L)
	Sodium	70 (3,0 mEq/L)
Other contaminants		
	Antimony	0,006
	Arsenic	0,005
	Barium	0,1
	Beryllium	0,0004
	Cadmium	0,001
	Chromium	0,014
	Mercury	0,0002
	Selenium	0,09
	Silver	0,005
	Thallium	0,002

[a] The physician has the ultimate responsibility for ensuring the quality of water used for dialysis.

[b] Unless otherwise noted.

4.1.3 Requirements for microbial contaminates in water

Product water used to prepare dialysate or concentrates from powder at a dialysis facility shall contain a total viable microbial count lower than 100 CFU/mL (when tested in accordance to clause 7.2.3) and an endotoxin concentration lower than 0,25 EU/mL (when tested in accordance to clause 7.2.4). The action level for the total viable microbial count in the product water shall be 50 CFU/mL. If this action level is observed in the product water, corrective measures shall promptly be taken to reduce the level. The manufacturer or supplier of a complete water treatment and distribution system shall demonstrate that the complete water treatment, storage, and distribution system is capable of meeting the requirements of this section at the time of installation.

Following installation of a water treatment, storage, and distribution system, the user is responsible for continued monitoring of the water bacteriology of the system and for complying with the requirements of this standard, including those requirements related to action levels.

4.2 Requirements for concentrate

4.2.1 Requirements for chemical and microbiological contaminants in concentrate

Users do not have to test concentrates to demonstrate compliance with the requirements of this clause when using commercially available packaged chemicals intended for use in preparing liquid concentrates at a dialysis facility or when using commercially available liquid concentrates, provided that the concentrates are manufactured in accordance with the requirements of ISO 13958. If the concentrate is made from raw chemicals the resulting concentrate should meet the requirements of ISO 13958.

4.2.2 Requirements for bicarbonate concentrate

Bicarbonate concentrate can grow bacteria, caution must be used to limit the bacterial levels in bicarbonate concentrate.

4.2.3 Requirements for water used to prepare concentrate

Water used to prepare concentrates at a dialysis facility shall meet the requirements of this standard. Any concentrate prepared at a dialysis facility should be capable of allowing the dialysis machine to prepare dialysate meeting the recommendations of this standard.

4.3 Requirements for dialysate

4.3.1 Microbiological contaminates in dialysate

4.3.1.1 General

The requirements contained in this clause apply to a sample of the dialysate collected at the inlet to the dyaliser or the reinfusion point.

4.3.1.2 Microbiological requirements for standard dialysate

Dialysate should contain a total viable microbial count lower than 100 CFU/mL (when tested in accordance to clause 6.3.3) and an endotoxin concentration of lower than 0,25 EU/mL (when tested in accordance to clause 6.3.4). The action level for the total viable microbial count in dialysate should be 50 CFU/mL.

NOTE If microbial counts exceeding the action levels are observed in the dialysate, corrective measures, such as disinfection and retesting, should promptly be taken to reduce the levels.

4.3.1.3 Microbiological requirements for ultrapure dialysate

Ultrapure dialysate shall contain a total viable microbial count lower than 0,1 CFU/mL (when tested in accordance to clause 6.3.3) and an endotoxin concentration lower than 0,03 EU/mL (when tested in accordance to clause 6.3.4). If those limits are exceeded in ultrapure dialysate, corrective measures shall be taken to reduce the levels