INTERNATIONAL STANDARD

ISO 13959

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Water for haemodialysis and related therapies

Eau pour hémodialyse et thérapies apparentées

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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.

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 13959 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 the first edition (ISO 13959:2002), which has been technically revised.

Introduction

Assurance of adequate water quality is one of the most important aspects of ensuring a safe and effective delivery of haemodialysis, haemodiafiltration or haemofiltration.

This International Standard contains minimum requirements, chemical and microbiological, for the water to be used for preparation of dialysis fluids, concentrates and for the re-use of haemodialysers and the necessary steps to assure compliance with those requirements. Haemodialysis and haemodiafiltration can expose the patient to more than 500 l of water per week across the semi-permeable membrane of the haemodialyser or haemodiafilter. Healthy individuals seldom have a weekly oral intake above 12 l. This over 40-fold increase in exposure requires control and monitoring of water quality to avoid excesses of known or suspected harmful substances. Since knowledge of potential injury from trace elements and contaminants of microbiological origin over long periods is still growing and techniques for treating drinking water are continuously developed, this International Standard will evolve and be refined accordingly. The physiological effects attributable to the presence of organic contaminants in dialysis water are important areas for research. At the time this International Standard was published it was premature to specify threshold values for organic contaminants below those published by various regulatory authorities.

The final dialysis fluid is produced from concentrates or salts manufactured, packaged and labelled according to ISO 13958 mixed with water meeting the requirements of this International Standard. Operation of water treatment equipment and haemodialysis systems, including ongoing monitoring of the quality of water used to prepare dialysis fluids, and handling of concentrates and salts are the responsibility of the haemodialysis facility and are addressed in ISO 23500. Haemodialysis professionals make choices about the various applications (haemodialysis, haemodiafiltration, haemofiltration) and should understand the risks of each and the requirements for safety for fluids used for each.

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

— “shall” means that compliance with a requirement or a test is mandatory for compliance with this International Standard;

— “should” means that compliance with a requirement or a test is recommended but is not mandatory for compliance with this International Standard; and

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

This International Standard is directed towards manufacturers and providers of water treatment systems and also to haemodialysis facilities.

Water for haemodialysis and related therapies

1 Scope

This International Standard specifies minimum requirements for water to be used in the preparation of concentrates, dialysis fluids for haemodialysis, haemodiafiltration and haemofiltration and for the reprocessing of haemodialysers.

This International Standard does not address the operation of water treatment equipment nor the final mixing of treated water with concentrates to produce the dialysis fluids used in such therapies. That operation is the sole responsibility of dialysis professionals.

This International Standard does not apply to dialysis fluid regenerating systems.

2 Terms and definitions

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

2.1
action level
concentration of a contaminant at which steps should be taken to interrupt the trend toward higher, unacceptable levels

2.2
chlorine, total
sum of free and combined chlorine

NOTE chlorine can exist in water as dissolved molecular chlorine (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.

2.3
colony-forming unit
CFU
measure of bacterial or fungal cell numbers that theoretically arise from a single cell or group of cells when grown on solid media

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

2.4
dialysis fluid
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 document to mean the fluid made from dialysis water and concentrates which is delivered to the dialyser by the dialysis fluid delivery system. Such phrases as “dialysate,” “dialysis solution,” or “dialysing fluid” can 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 hemofiltration.

2.5
dialysis water
water that has been treated to meet the requirements of this International Standard 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

2.6
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** (2.12)].

2.7
endotoxin units
EU
units assayed by the *Limulus* amoebocyte lysate (LAL) test when testing for endotoxins

NOTE 1 Because the 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 1983 harmonization of endotoxin assays, EU and IU are equivalent.

2.8
feed water
water supplied to a water treatment system or an individual component of a water treatment system

2.9
***Limulus* amoebocyte lysate test**
LAL
assay used to detect endotoxin

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

2.10
microbial
referring to microscopic organisms, bacteria, fungi and so forth

2.11
microbial 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)

2.12
pyrogen
fever-producing substance

NOTE Pyrogens are most often lipopolysaccharides of gram-negative bacterial origin [see also **endotoxin** (2.6)].

3 Dialysis water requirements

3.1 Dialysis water verification and monitoring

The quality of the dialysis water, as specified in 3.2 and 3.3, shall be verified upon installation of a water treatment system. Monitoring of the dialysis water quality shall be carried out thereafter.

3.2 Microbiological requirements

Total viable microbial counts in dialysis water shall be less than 100 CFU/ml, or lower if required by national legislation or regulations. An action level shall be set based on knowledge of the microbial dynamics of the system. Typically, the action level will be 50 % of the maximum allowable level.

Endotoxin content in dialysis water shall be less than 0,25 EU/ml, or lower if required by national legislation or regulations. An action level shall be set, typically at 50 % of the maximum allowable level.

NOTE See Clause A.1 for a history of these requirements.

3.3 Chemical contaminants

Dialysis water shall not contain chemicals at concentrations in excess of those listed in Tables 1 and 2, or as required by national legislation or regulations.

NOTE See Clause A.2 for explanation of values supplied.

Where the dialysis water is used for the reprocessing of haemodialysers, (cleaning, testing and mixing of disinfectants) the user is cautioned that the dialysis water shall meet the requirements of this International Standard. The dialysis water should be measured at the input to the dialyser reprocessing equipment.

Table 1 — Maximum allowable levels of toxic chemicals and dialysis fluid electrolytes in dialysis water [a]

Contaminant	Maximum concentration mg/l[b]
Contaminants with documented toxicity in haemodialysis	
Aluminium	0,01
Total chlorine	0,1
Copper	0,1
Fluoride	0,2
Lead	0,005
Nitrate (as N)	2
Sulfate	100
Zinc	0,1
Electrolytes normally included in dialysis fluid	
Calcium	2 (0,05 mmol/l)
Magnesium	4 (0,15 mmol/l)
Potassium	8 (0,2 mmol/l)
Sodium	70 (3,0 mmol/l)

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

[b] Unless otherwise noted.

Table 2 — Maximum allowable levels of trace elements in dialysis water

Contaminant	Maximum concentration mg/l
Antimony	0,006
Arsenic	0,005
Barium	0,1
Beryllium	0,000 4
Cadmium	0,001
Chromium	0,014
Mercury	0,000 2
Selenium	0,09
Silver	0,005
Thallium	0,002

4 Tests for compliance with microbiological and chemical requirements

4.1 Microbiology of dialysis water

Samples shall be collected where a dialysis machine connects to the water distribution loop, from a sample point in the distal segment of the loop or where water enters a mixing tank.

Samples shall be assayed within 4 h of collection, or be immediately refrigerated and assayed within 24 h of collection on a regular schedule. Total viable counts (standard plate counts) shall be obtained using conventional microbiological assay procedures (pour plate, spread plate, membrane filter techniques). Membrane filtration is the preferred method for this test. The calibrated loop technique is not accepted.

Culture media should be tryptone glucose extract agar (TGEA), Reasoners 2A (R2A), or other media that can be demonstrated to provide equivalent results. Blood agar and chocolate agar shall not be used. Incubation temperatures of 17 °C to 23 °C and incubation time of 168 h (7 d) are recommended. Other incubation times and temperatures may be used if it can be demonstrated that they provide equivalent results. No method will give a total microbial count.

The presence of endotoxins shall be determined by the *Limulus* amoebocyte lysate (LAL) test. Other test methods may be used if it can be demonstrated that they provide equivalent results.

4.2 Chemical contaminants test methods

Compliance with the requirements listed in Table 1 can be shown by using chemical analysis methods referenced by the American Public Health Association [3], methods referenced by the U.S. Environmental Protection Agency [46], methods referenced in applicable pharmacopoeia, and/or other equivalent validated analytical methods.

Compliance with the requirements listed in Table 2 can be shown in one of three ways.

— Where such testing is available, the individual contaminants in Table 2 can be determined using chemical analysis methods referenced by the American Public Health Association [3], methods referenced by the U.S. Environmental Protection Agency [46], and/or other equivalent analytical methods.

— Where testing for the individual trace elements listed in Table 2 is not available, and the source water can be demonstrated to meet the standards for potable water as defined by the WHO or local regulations, an analysis for total heavy metals can be used with a maximum allowable level of 0,1 mg/l.

— If neither of these options is available, compliance with the requirements of Table 2 can be met by using water that can be demonstrated to meet the potable water requirements of the WHO (see Reference [51]) or local regulations and a reverse osmosis system with a rejection of > 90 % based on conductivity, resistivity or TDS. Samples shall be collected at the end of the water purification cascade or at the most distal point in each water distribution loop.

Table 3 lists tests for each contaminant, along with an appropriate reference.

Table 3 — Analytical tests for chemical contaminants

Contaminant	Test name	Reference, test number
Aluminium	Atomic absorption (electrothermal)	American Public Health Assn, #3113
Antimony	Atomic absorption (platform)	US EPA, #200.9
Arsenic	Atomic absorption (gaseous hydride)	American Public Health Assn, #3114
Barium	Atomic absorption (electrothermal)	American Public Health Assn, #3113
Beryllium	Atomic absorption (platform)	US EPA, #200.9
Cadmium	Atomic absorption (electrothermal)	American Public Health Assn, #3113
Calcium	EDTA titrimetric method or atomic absorption (direct aspiration) or ion specific electrode or inductively-coupled plasma spectrometry (direct aspiration)	American Public Health Assn, #3500-Ca D American Public Health Assn, #3111B
Total chlorine	DPD ferrous titrimetric method or DPD colorimetric method	American Public Health Assn, #4500-Cl F American Public Health Assn, #4500-Cl G
Chromium	Atomic absorption (electrothermal)	American Public Health Assn, #3113
Copper	Atomic absorption (direct aspiration) or neocuproine method	American Public Health Assn, #3111 American Public Health Assn, #3500-Cu D
Fluoride	Ion selective electrode method or sodium 2-(parasulfophenylazo)-1,8-dihydroxy-3,6-naphthalenedisulfonate (SPADNS) method	American Public Health Assn, #4500-F^- C American Public Health Assn, #4500-F^- D
Lead	Atomic absorption (electrothermal)	American Public Health Assn, #3113
Magnesium	Atomic absorption (direct aspiration) or inductively-coupled plasma spectrometry (direct aspiration)	American Public Health Assn, #3111
Mercury	Flameless cold vapour technique (atomic absorption)	American Public Health Assn, #3112
Nitrate	Cadmium reduction method	American Public Health Assn, #4500-NO_3 E
Potassium	Atomic absorption (direct aspiration) or flame photometric method or ion specific electrode or inductively-coupled plasma spectrometry (direct aspiration)	American Public Health Assn, #3111 American Public Health Assn, #3500-K D American Public Health Assn, #3500-K E