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

Part 3: Water for haemodialysis and related therapies

Préparation et management de la qualité des liquides d'hémodialyse et de thérapies annexes —
Partie 3: Eau pour hémodialyse et thérapies apparentées

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Contents

Page

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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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 23500-3:2019), which has been technically revised.

The main changes are as follows:

— the use of WHO Drinking Water Guideline as the drinking water quality reference has replaced the previously used EPA Water quality requirements;

— thallium has been removed from the list of contaminants of other trace elements in dialysis water as no published study reports that this contaminant is of particular concern in the setting of haemodialysis;

— alternatives to classic microbial analytical methods (endotoxin testing using recombinant Factor C [rFC]) have been incorporated.

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

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 document contains the minimum chemical and microbiological requirements for the water to be used for preparation of dialysis fluids and concentrates, and for the reprocessing of haemodialysers and the necessary steps to ensure conformity with those requirements.

Haemodialysis and related therapies such as 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 regular surveillance 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 document will evolve and be refined accordingly. The physiological effects attributable to the presence of organic contaminants in dialysis water are important areas for research, however, the effect of such contaminants on patients receiving regular dialysis treatment is largely unknown, consequently no threshold values for organic contaminants permitted in water used for the preparation of dialysis fluids, concentrates and reprocessing of haemodialysers has been specified in this document.

Within this document, current measurement techniques at the time of publication have been cited. Other standard methods can be used, provided that such methods have been appropriately validated and are comparable to the cited methods.

The final dialysis fluid is produced from concentrates or salts manufactured, packaged and labelled according to ISO 23500-4 mixed with water meeting the requirements of this document. The operation of water treatment equipment and haemodialysis systems, including ongoing surveillance 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 23500-1. 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.

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

The rationale for the development of this document is given in Annex A.

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

Part 3:
Water for haemodialysis and related therapies

1 Scope

This document specifies the minimum chemical and microbiological quality requirements, for water used for preparation of dialysis fluids, concentrates, and for the reprocessing of haemodialysers, together with the necessary steps to ensure conformity with the requirements. The document also provides guidance for the ongoing monitoring of the purity of such water in terms of chemical and microbiological quality.

This document is applicable to

— water used in the preparation of dialysis fluids for haemodialysis, haemodiafiltration and haemofiltration and the reprocessing of haemodialysers, and

— water used in the preparation of concentrates.

This document does not apply to dialysis fluid regenerating systems.

The operation of water treatment equipment and the final mixing of treated water with concentrates to produce dialysis fluid are the sole responsibility of dialysis professionals.

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 23500-1, *Preparation and quality management of fluids for haemodialysis and related therapies — Part 1: General requirements*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 23500-1 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/

4 Requirements

4.1 Dialysis water quality requirements

The quality of the dialysis water, as specified in 4.2 and 4.3, shall be verified upon installation of a water treatment system. Regular surveillance of the dialysis water quality shall be carried out thereafter.

NOTE Throughout this document, it is assumed that the water undergoing treatment is potable water and therefore meets the appropriate regulatory requirements for such water. If the water supply is derived from an alternate source such as a privately-owned borehole or well, contaminant levels cannot be as rigorously controlled.

4.2 Chemical contaminant requirements

4.2.1 General

Dialysis water shall not contain chemicals at concentrations in excess of those listed in Tables 1 and 2. Table 1 does not include any recommendation for organic carbon, pesticides and other chemicals such as pharmaceutical products and endocrine disruptors that can be present in feed water. It is technically difficult and costly to measure such substances on a routine basis. The effect of their presence on haemodialysis patients is difficult to specify and consequences of exposure are probably of a long-term nature. Furthermore, there is an absence of evidence of their widespread presence in water although it is recognized that inadvertent discharges are possible. In view of this, it is not at present possible to specify limits for their presence in water used in the preparation of dialysis fluid.

Nanofiltration and reverse osmosis are capable of significant rejection of many such compounds. Granular activated carbon (GAC) is also highly effective at removing majority of these chemicals. However, as granular activated carbon is widely used in the removal chlorine/chloramine, their use in the removal of organic carbons, pesticides and other chemicals will be dependent upon the size of the carbon filters and/or beds and users shall be aware of appropriate dimensioning since the majority of carbon valences can be already occupied and not available for further removal activity.

NOTE 1 See Clause A.3 for an explanation of the values in Tables 1 and 2.

NOTE 2 The maximum allowable levels of contaminants listed in Tables 1 and 2 include the anticipated uncertainty associated with the analytical methodologies listed in Table 4.

Where the dialysis water is used to reprocess haemodialysers (cleaning, testing and mixing of disinfectants), the user is cautioned that the dialysis water shall meet the requirements of this document. 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[b] mg/l
Contaminants with documented toxicity in haemodialysis	
Aluminium	0,01
Total chlorine[c]	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] A physician in charge of dialysis has the ultimate responsibility for ensuring the quality of water used for dialysis.

[b] The reader is cautioned to refer to the latest edition of this document to ensure that there have been no changes to this table.

[b] Unless otherwise indicated.

[c] When chlorine is added to water, some of the chlorine reacts with organic materials and metals in the water and is not available for disinfection (i.e. the chlorine demand of the water). The remaining chlorine is the total chlorine and is the sum of free or non-bound chlorine and combined chlorine.

Total chlorine is usually measured on site by appropriately trained personnel in water prior to entering the treatment system. Additional measurements in the treated water are not necessary provided that the pre-treatment concentration level is below the permitted limit.

There is no direct method for the measurement of chloramine. It is generally established by measuring total and free chlorine concentrations and calculating the difference. When total chlorine tests are used as a single analysis the maximum level for both chlorine and chloramine shall not exceed 0,1 mg/l. Since there is no distinction between chlorine and chloramine, this safely assumes that all chlorine present is chloramine.

NOTE The maximum allowable levels of contaminants listed include the anticipated uncertainty associated with the analytical methodologies used to establish the values shown.

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

Contaminant	Maximum concentration[a] 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

[a] The reader is cautioned to refer to the latest edition of this document to ensure that no changes have been made to the maximum concentrations shown.

NOTE The maximum allowable levels of contaminants listed in include the anticipated uncertainty associated with the analytical methodologies to establish the values shown.

4.2.2 Organic carbon, pesticides and other chemicals

The presence of organic compounds, such as pesticides, polycyclic aromatic hydrocarbons and other chemicals such as pharmaceutical products and endocrine disruptors in respect of haemodialysis patients are difficult to specify. Consequences of exposure are probably of a long-term nature and it is technically difficult and costly to measure these substances on a routine basis. Furthermore, there is an absence of evidence of their widespread presence in water although it is recognized that inadvertent discharges are possible. In view of this, it is at present not possible to specify limits for their presence in water used in the preparation of dialysis fluid.

4.3 Dialysis water microbiological requirements

Total viable microbial counts in dialysis water shall be less than 100 CFU/ml. 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. An action level shall be set, typically at 50 % of the maximum allowable level.

Fungi (yeasts and filamentous fungi) can coexist with bacteria and endotoxin in the dialysis water. Further studies on the presence of fungi in haemodialysis water systems, their role in biofilm formation and their clinical significance are required and in view of this, no recommendation in respect of permitted maximum limits is made.

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 and non-pyrogenic concentrates and by utilising sterile and non-pyrogenic dialysis fluid pathway, ultrapure dialysis fluid can be produced in such integrated and validated systems.

NOTE See Clause A.4 for a history of these requirements.

5 Tests for microbiological and chemical requirements

5.1 Dialysis water microbiology

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

Samples should be analysed as soon as possible after collection to avoid unpredictable changes in the microbial population. If samples cannot be analysed within 4 h of collection, they should be stored at <10 °C without freezing until ready to transport to the laboratory for analysis. Sample storage for more than 24 h should be avoided and sample shipping should be done according to the laboratory's instructions.

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. Other methods may be used, provided that such methods have been appropriately validated and are comparable to the cited methods. The use of the calibrated loop technique is not acceptable.

5.2 Microbial contaminant test methods

Methodology to establish microbial contaminant levels is given in Table 3. Such methods provide only a relative indication of the bioburden rather than an absolute measure.

Recommended methods and cultivation conditions can also be found in ISO 23500-4 and ISO 23500-5 as well as this document (see Table 3). The methodology detailed uses tryptone glucose extract agar (TGEA) and Reasoner's agar no. 2 (R2A) incubated at 17 °C to 23 °C for 7 d and tryptic soy agar (TSA) at an incubation temperature of 35 °C to 37 °C and an incubation time of 48 h.[17] The background for the inclusion of TSA for dialysis water and dialysis fluid used for standard dialysis is explained in Clause A.4.