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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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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.

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 documents 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).

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. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

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*.

This first edition cancels and replaces ISO 13959:2014, which has been technically revised. The main changes compared to the previous edition are as follows:

— The document forms part of a revised and renumbered series dealing with the preparation and quality management of fluids for haemodialysis and related therapies. The series comprise ISO 23500-1 (previously ISO 23500), ISO 23500-2, (previously ISO 26722), ISO 23500-3, (previously ISO 13959), ISO 23500-4, (previously ISO 13958), and ISO 23500-5, (previously ISO 11663).

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 minimum requirements, chemical and microbiological, for the water to be used for preparation of dialysis fluids, 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 revised document.

Within this document, measurement techniques current 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. Operation of water treatment equipment and haemodialysis systems, including on-going 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 informative 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 minimum requirements for water to be used in haemodialysis and related therapies.

This document includes water to be used in the preparation of concentrates, dialysis fluids for haemodialysis, haemodiafiltration and haemofiltration, and for the reprocessing of haemodialysers.

This document excludes the operation of water treatment equipment and the final mixing of treated water with concentrates to produce dialysis fluid. Those operations are the sole responsibility of dialysis professionals. This document does not apply to dialysis fluid regenerating systems.

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 terminological databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at http://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, or as required by national legislation or regulations. Table 1 does not include any recommendation in respect of 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 define 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 define 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 or 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 A.3 for an explanation of values supplied.

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 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 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 mg[b]
Contaminants with documented toxicity in haemodialysis	
Aluminium	0,01
Total chlorine[1]	0,1
Copper	0,1
Fluoride	0,2
Lead	0,005
Nitrate (as N)	2
Sulfate	100
Zinc	0,1

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

[b] Unless otherwise indicated.

[1] 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 (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.

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.

Table 1 *(continued)*

Contaminant	Maximum concentration mg[b]
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 ultimate responsibility for ensuring the quality of water used for dialysis.

[b] Unless otherwise indicated.

[1] 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 (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.

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.

Table 2 — Maximum allowable levels of other 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

4.2.2 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 define. 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 define 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, 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.

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.

NOTE See 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 in accordance with 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 bacterial 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 (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 a period of 7 days and Tryptic Soy Agar (TSA) at an incubation temperature of 35 °C to 37 °C and an incubation time of 48 h[8]. The background for the inclusion of TSA for standard water and standard dialysis fluid used for standard dialysis is explained in detail in A.4.

Different media types and incubation periods can result in varying colony concentrations and types of microorganisms recovered[8][9][10]. The use of Reasoner's 2A agar (R2A) has been shown in previous studies to result in higher colony counts than tryptic soy agar (TSA) for water and dialysis fluids samples[10][11][12]. In a more recent publication, in 2016, the authors indicated that there were no significant differences for comparisons of bacterial burden of standard dialysis water and standard dialysis fluid yielding colony counts ≥50 CFU/ml when assayed using R2A and TSA at the conditions stated in the preceding paragraph of this subclause [8].

Historic studies with tryptone glucose extract agar (TGEA) incubated at 17 °C to 23 °C for a period of 7 days also yielded higher colony counts than TSA.[13] Maltais et al.[8] in their comparison of this medium with TSA showed that the proportion of standard dialysis water samples yielding colony counts ≥50 CFU/ml was significantly different from that found using TSA at an incubation temperature of 35 °C to 37 °C and an incubation time of 48 hours (p = 0,001). The proportions of dialysis fluid samples in which microbial burden was ≥50 CFU/ml were not significantly different on the two media and incubation conditions.

The culture medium and incubation times selected should be based on the type of fluid to be analysed e.g. standard dialysis fluid, water used in the preparation of standard dialysis fluid, ultrapure dialysis fluid, water used for the preparation of ultrapure dialysis fluid or fluid used for online therapies such as haemodiafiltration. The method selected, should be based on the analysis of the advantages, disadvantages and sensitivity, of each of the methods detailed above. According to the United States

Pharmacopeia, “the decision to use longer incubation times", should be made after balancing the need for timely information and the type of corrective actions required when alert or action level is exceeded with the ability to recover the microorganisms of interest. The advantages gained by incubating for longer times namely recovery of injured microorganisms, slow growers, or more fastidious microorganisms, should be balanced against the need to have a timely investigation and take corrective action, as well as the ability of these microorganisms to detrimentally affect products or processes” [e.g. patient safety].

Other methods may be used, provided that such methods have been appropriately validated and are comparable to the cited methods. Blood agar and chocolate agar shall not be used.

Currently there are no requirements for routine surveillance for the presence of fungi (i.e. yeasts and filamentous fungi) which can coexist with other microbial species, however if indication of their presence is required, membrane filtration is the preferred method for the provision of a sample suitable for analysis. Culture media used should be Sabouraud, or Malt Extract Agar (MEA) media. Other methods may be used, provided that such methods have been appropriately validated and are comparable to the cited methods. An incubation temperature of 17 °C to 23 °C and an incubation time of 168 h (7 d) are recommended. Other incubation times and temperatures can be used, provided it has been demonstrated that such methods have been appropriately validated and are comparable to the cited methods.

The presence of endotoxins shall be determined by a *Limulus* amoebocyte lysate (LAL) assay or other validated method.

Table 3 — Culture techniques

Culture medium	Incubation temperature	Incubation time
Tryptone Glucose Extract Agar (TGEA)	17 °C to 23 °C	7 d
Reasoner's Agar no. 2 (R2A)	17 °C to 23 °C	7 d
Sabouraud or Malt Extract Agar[a]	17 °C to 23 °C	7 d
Tryptic Soy Agar (TSA) [b]	35 °C to 37 °C	48 h

[a] Intended for the quantification of yeasts and filamentous fungi. Currently there are no requirements in this document for their routine surveillance; they have been included for completeness.

[b] The use of TSA has been only validated for measurement of standard dialysis water.

5.3 Chemical contaminants test methods

Conformity with the requirements listed in Table 1 can be shown by using chemical analysis methods referenced by the ISO[1][2][3], the American Public Health Association[4] or the US Environmental Protection Agency[5][6] methods referenced in applicable pharmacopoeia, or by any other equivalent validated analytical method.

Conformity to the requirements listed in Table 2 can be shown in one of the three ways below.

— Where such testing is available, the individual contaminants in Table 2 can be determined using chemical analysis methods referenced by ISO[1][2][3], the American Public Health Association[4] or the US Environmental Protection Agency[5][6], 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[7], 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, conformity 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 or local regulations and a reverse osmosis system with a rejection of > 90 % based on conductivity,