INTERNATIONAL STANDARD

ISO 23500-5

First edition
2019-02

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

Part 5: Quality of dialysis fluid for haemodialysis and related therapies

Préparation et management de la qualité des liquides d'hémodialyse et de thérapies annexes —

Partie 5: Qualité des liquides de dialyse pour hémodialyse et thérapies apparentées

Reference number
ISO 23500-5:2019(E)

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Published in Switzerland

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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 11663:2014, 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

Haemodialysis patients are directly exposed to large volumes of dialysis fluid, with the dialyser membrane being the only barrier against transfer of hazardous contaminants from the dialysis fluid to the patient. It has long been known that there could be hazardous contaminants in the water and concentrates used to prepare the dialysis fluid. To minimize this hazard, ISO 23500-3 and ISO 23500-4 set forth quality requirements for the water and concentrates used to prepare dialysis fluid. However, if the dialysis fluid is not prepared carefully, it could contain unacceptable levels of contaminants even though it is prepared from water and concentrates, conforming to the requirements of ISO 23500-3 and ISO 23500-4. Further, the dialysis fluid might be used as the starting material for the online preparation of fluids intended for infusion into the patient, for example, in therapies such as online haemodiafiltration. For these reasons, this document for dialysis fluid quality was developed to complement the existing International Standards for water and concentrates, ISO 23500-3 and ISO 23500-4, respectively. Guidelines to aid the user in routinely meeting the requirements of this document and ISO 23500-3 can be found in ISO 23500-1.

Within these International Standards, measurement techniques current at the time of preparation 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 rationale for the development of this document is given in Annex A.

This document reflects the conscientious efforts of healthcare professionals, patients, and medical device manufacturers to develop recommendations for the quality of dialysis fluid. This document is directed at the healthcare professionals involved in the management of dialysis facilities and the routine care of patients treated in dialysis facilities, since they are responsible for the final preparation of dialysis fluid. The recommendations contained in this document are not intended for regulatory application.

This document aims to help protect haemodialysis patients from adverse effects arising from known chemical and microbiological contaminants that can 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 applicable quality standards.

The concepts incorporated in this document should not be considered inflexible or static. The requirements and 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.

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

Part 5: Quality of dialysis fluid for haemodialysis and related therapies

1 Scope

This document specifies minimum quality requirements for dialysis fluids used in haemodialysis and related therapies.

This document includes dialysis fluids used for haemodialysis and haemodiafiltration, including substitution fluid for haemodiafiltration and haemofiltration.

This document excludes the water and concentrates used to prepare dialysis fluid or the equipment used in its preparation. Those areas are covered by other International Standards.

Sorbent-based dialysis fluid regeneration systems that regenerate and recirculate small volumes of dialysis fluid, systems for continuous renal replacement therapy that use pre-packaged solutions, and systems and solutions for peritoneal dialysis are excluded from this document.

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*

ISO 23500-3, *Preparation and quality management of fluids for haemodialysis and related therapies — Part 3: Quality of water for haemodialysis and related therapies*

ISO 23500-4, *Preparation and quality management of fluids for haemodialysis and related therapies — Part 4: Concentrates for haemodialysis and related therapies*

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 Microbiological contaminants in dialysis fluid

4.1.1 General

The requirements contained in this clause apply to a sample of the dialysis fluid collected at the inlet to the dialyser or the reinfusion point.

4.1.2 Microbiological requirements for standard dialysis fluid

Standard dialysis fluid shall contain a total viable microbial count of less than 100 CFU/ml (when tested in accordance with Clause 5) and an endotoxin concentration of less than 0,5 EU/ml (when tested in accordance with Clause 5).

Action levels for the total viable microbial count and endotoxin concentration in dialysis fluid should also be set based on knowledge of the microbial dynamics of the system. Typically, the action levels are set at 50 % of the maximum allowable levels for total viable microbial count and endotoxin; other levels can be set.

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

Associated with the presence of bacteria and endotoxin in dialysis fluid is the likely presence of fungi (yeasts and filamentous fungi). After extensive discussion, the working group has not recommended maximum limits, for such contaminants.

Tests for bacterial growth and endotoxins are not required if the dialysis machine fluid pathway is fitted with an appropriate capacity bacteria-retentive and endotoxin-retentive filter validated by the manufacturer and operated and surveilled according to the manufacturer's instructions, unless the manufacturer requires such tests in the instructions for use.

4.1.3 Microbiological requirements for ultrapure dialysis fluid

Ultrapure dialysis fluid shall contain a total viable microbial count of less than 0,1 CFU/ml (when tested in accordance with Clause 5) and an endotoxin concentration less than 0,03 EU/ml (when tested in accordance with Clause 5). If those limits are exceeded in ultrapure dialysis fluid, corrective measures should be taken to reduce the levels to an acceptable level. The user is responsible for surveilling the dialysis fluid bacteriology of the system following installation. It is incumbent on the user to establish a regular surveillance routine.

Tests for bacterial growth and endotoxins are not required if the dialysis machine fluid pathway is fitted with an appropriate capacity bacteria-retentive and endotoxin-retentive filter validated by the manufacturer and operated and surveilled according to the manufacturer's instructions, unless the manufacturer requires such tests in the instructions for use.

4.1.4 Microbiological requirements for online prepared substitution fluid

The requirements contained in this clause apply to online prepared fluid intended to be infused into the patient as it enters the patient's blood.

This fluid shall be sterile and nonpyrogenic.

Substitution fluid for convective therapies, such as haemodiafiltration and haemofiltration, can be produced online by a process of ultrafiltration with bacteria-retentive and endotoxin-retentive filters. This online process shall be validated to produce fluid that is sterile and nonpyrogenic.

Conformity of online produced fluid with the requirements of this document cannot be demonstrated with traditional test procedures. For this reason, conformity with this document shall be ensured by

proper operation of a validated system, verified according to the manufacturer's instructions at the time of installation, and confirmed by the user with a regular surveillance and maintenance schedule. The user shall follow the manufacturer's instructions for use of the validated system, and the user's surveillance and maintenance schedule shall be designed to confirm that the water and concentrates used to prepare the substitution fluid continue to meet the specifications of ISO 23500-3 and ISO 23500-4.

4.2 Chemical contaminants in dialysis fluid

Dialysis fluid shall be prepared from water meeting the requirements of ISO 23500-3 and acid and bicarbonate concentrates meeting the requirements of ISO 23500-4. The water and concentrates shall be combined using individual dialysis fluid delivery systems or a central dialysis fluid delivery system constructed from materials that do not contribute chemical contaminants to the final dialysis fluid.

The maximum levels of chemical contaminants permitted in water used to prepare dialysis fluid and concentrates are given in ISO 23500-3 and are also shown in informative Annex B of this document (Tables B.1 and B.2) together with methods of determination (Table B.3). Other equivalent analytical methods can be used. Where testing for the individual trace elements listed in Table B.2 is not available, an analysis for total heavy metals can be used with a maximum allowable level of at 0,1 mg/l.

5 Tests for conformity with microbiological requirements

5.1 Sampling

In some newer dialysis machines, dialysis fluid flow stops when the effluent line is disconnected from the dialyser. In these instances, the machines are equipped with dialysis fluid sampling ports that can be accessed using a syringe. Sample ports can be disinfected with alcohol and allowed to air-dry. A sterile syringe should be used to aspirate at least 10 ml of dialysis fluid out of the sampling port. The filled syringe is discarded and a fresh sample of dialysis fluid collected using a new sterile syringe. For sample ports consisting of a simple septum penetrated with a needle, the use of a second syringe is not necessary. Alternatively, if the dialysis machine permits, samples can be collected immediately before the dialyser by disconnecting the inlet connector and aseptically collecting a "free/clean" catch sample after allowing dialysis fluid to run for at least 60 s unless manufacturers' instructions state otherwise.

Microbial analysis of any fluid sample should be conducted 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 and during transit to the laboratory. Sample storage for more than 24 h should be avoided, and sample shipping should be in accordance with the laboratory's instructions.

5.2 Culture methods

Accurate microbiological surveillance is important in the indication of the microbial content of dialysis water and dialysis fluid. Culture results obtained using the methods outlined in this document and summarized in Table 1 are only a relative indicator of the bioburden and do not provide an absolute measure of the absolute bacterial burden.

Total viable microbial counts (standard plate counts) shall be obtained using conventional microbiological assay procedures (pour plate, spread plate, membrane filter techniques). The calibrated loop technique shall not be used.

Preferred methods and sample volumes:

Standard dialysis fluid:

— spread plate, 0,1 ml to 0,3 ml;

— pour plate, typically 1 ml.

Ultrapure dialysis fluid:

— membrane filtration, 10 ml to 1 000 ml.

Substitution fluid:

— sterility cannot be proven by sampling.

Different media types and incubation periods can result in varying colony concentrations and types of microorganisms recovered.

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[6][7]. In a more recent publication, 2016[8], 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 Table 1.

Tryptone glucose extract agar (TGEA) incubated at 17 °C to 23 °C for a period of 7 days in previous studies also yielded higher colony counts than TSA[9]. Maltais et al. 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[8].

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 on line therapies such as haemodiafiltration. The method selected should be based on the analysis of the advantages, disadvantages and sensitivity of each of the suggested methods. It should also ensure that patient safety is safeguarded and allow for consideration of local laboratory working practices, and that local regulatory and reimbursement requirements can be met.

Blood agar and chocolate agar shall not be used.

Table 1 — 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
Tryptic Soy Agar (TSA)[a]	35 °C to 37 °C	48 h
[a] The use of TSA has been only validated for measurement of standard dialysis fluid.		

Other medium, incubation conditions and colony counting times can be used provided it has been demonstrated that such methods have been appropriately validated and are comparable to the cited methods.

Currently there are no requirements for routine surveillance for the presence of fungi (i.e. yeasts and filamentous fungi), however if quantification is required, membrane filtration is suggested as the method for obtaining a sample suitable for analysis. For culture, Sabouraud or Malt Extract Agar (MEA) are recommended.

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

Conformity with the microbial standards for ultrapure dialysis fluid and substitution fluid prepared online with a validated system can be met by following the requirements and instructions of the manufacturer of the dialysis fluid delivery system.

Annex A
(informative)

Rationale for the development and provisions of this document

A.1 Microbiological contaminants in dialysis fluid

NOTE The information in this clause is intended to give the reader a historical perspective of how the microbial limits were developed for this document.

Pyrogenic reactions are caused by lipopolysaccharides or endotoxins that are associated with gram-negative bacteria. Furthermore, gram-negative water bacteria have been shown to have the capability of multiplying rapidly in a variety of hospital-associated fluids, including distilled, deionized, reverse osmosis, and softened water, all of which have been used in the past as supply water for haemodialysis systems. The dialysis fluid, which is a balanced salt solution made with this water, likewise provides a very good growth medium for these types of bacteria. Several studies have demonstrated that the incidence of pyrogenic reactions can be related directly to the number of bacteria in dialysis fluid even at low levels of bacterial contamination, pyrogenic reactions have been reported when the source of endotoxin was exogenous to the dialysis system (i.e. present in the community water supply)[10][11][12][13].

Several investigators have shown that bacteria growing in dialysis fluid can produce products that cross dialysis membranes[14][15]. It has also been shown that gram-negative bacteria growing in dialysis fluid produced endotoxins, that in turn stimulated the production of anti-endotoxin antibodies in haemodialysis patients[16][17]. These data suggest that endotoxins do indeed cross dialysis membranes, either intact or as fragments. The use of the very permeable membranes known as high-flux membranes has raised the possibility of a greater likelihood of passage of endotoxins into the blood path. Several studies support this contention. Vanholder et al. observed an increase in plasma endotoxin concentrations during dialysis against dialysis fluid containing 10^3 CFU/ml to 10^4 CFU/ml *Pseudomonas* species[18]. In vitro studies using both radiolabelled lipopolysaccharide and biological assays have demonstrated that biologically active substances derived from bacteria found in dialysis fluid can cross a variety of dialysis membranes[19] to [25]. Also, patients treated with high-flux membranes are reported to have higher levels of anti-endotoxin antibodies than normal subjects or patients treated with conventional low-flux membranes[26]. Finally, it was reported that the use of high-flux dialysers is a significant risk factor for pyrogenic reactions[27]. Although other investigators have not been able to demonstrate endotoxin transfer across dialysis membranes[28][29], the preponderance of reports now supports the ability of endotoxin to transfer across at least some high-flux membranes under some operating conditions. Furthermore, in a Japanese Society for Dialysis Therapy (JSDT) survey, the 1-year mortality rate was significantly higher at facilities with a dialysis fluid endotoxin concentration of >0,100 EU/ml[30][31]. Consequently, it seems prudent to impose an upper limit on the endotoxin content of dialysis water and dialysis fluid. A level of 2 EU/ml was chosen by AAMI in 2001 as the upper limit for endotoxin, since these levels were easily achieved with contemporary water treatment systems using reverse osmosis, ultrafiltration, or both. At the same time, the European Community chose to use 0,25 EU/ml as the maximum allowable level of endotoxin in dialysis water. When ISO 13959 was revised in 2009, the 0,25 EU/ml limit for dialysis water was included. In developing this document for dialysis fluid quality, the maximum allowable level of endotoxin was set at 0,5 EU/ml analysed by the *Limulus* amebocyte lysate test.

The level is set higher than that for dialysis water in recognition that both the water and concentrates used in the preparation of dialysis fluid can contribute endotoxin.

In addition to the acute risk of pyrogenic reactions, there is increasing indirect evidence that chronic exposure to low amounts of endotoxin might play a role in some of the long-term complications of haemodialysis therapy. Patients treated with ultrafiltered dialysis fluid have demonstrated a decrease in serum β_2-microglobulin concentrations, a decrease in markers of an inflammatory response

and oxidant stress, and an increased responsiveness to erythropoietin. In longer term studies, use of ultrafiltered dialysis fluid has been associated with a decreased incidence of β_2-microglobulin-associated amyloidosis, better preservation of residual renal function, and improved nutritional status[14][17][25][32] to [44].

These observations have led to the recommendation that dialysis fluid of a higher microbiological quality, so-called "ultrapure" dialysis fluid, should be used for routine haemodialysis[45]. Ultrapure dialysis fluid is defined as one having a bacterial content of less than 0,1 CFU/ml and an endotoxin content of less than 0,03 EU/ml using sensitive assays[46]. This definition is now widely accepted, particularly in Europe, as the standard for dialysis fluid used to prepare substitution solution for online convective therapies. In developing this document, the desirability of using ultrapure dialysis fluid was recognized, but it was accepted that obtaining this level of purity on a routine basis might not yet be feasible in all dialysis settings.

As up to 7 d can elapse between sampling dialysis fluid for the determination of microbiological contamination and the receipt of results depending on the analytical method used, and because bacterial proliferation can be rapid, action levels for microbial counts were introduced into this document. These action levels allow the user to initiate corrective action before levels exceed the maximum levels established by this document.

In haemodialysis, the net movement of water is from the blood to the dialysis fluid, although within the dialyser there can be movement of dialysis fluid to the blood due to the phenomenon of back-filtration, particularly in dialysers with highly permeable membranes[47]. In contrast, haemofiltration and haemodiafiltration feature infusions of large volumes of electrolyte solution (20 l to more than 100 l) into the blood. Increasingly, such solution is being prepared online from ultrapure dialysis fluid. The large volumes of fluid infused in haemofiltration and haemodiafiltration, and concerns about the transfer of endotoxin and endotoxin fragments across high-flux membranes, necessitate the use of such fluid to minimize patient risk.

A.2 Chemical contaminants in dialysis fluid

When this document was being developed, the need to include maximum levels for chemical contaminants in dialysis fluid was discussed. It was proposed that the maximum allowable levels of chemical contaminants in dialysis fluid should be the same as those in the water used to prepare the dialysis fluid since there were no data supporting the need for lower levels. Dialysis fluid is prepared from water and concentrates, meeting the requirements of ISO 23500-3:2019 and ISO 23500-4:2019, including the same requirements for maximum levels of chemical contaminants that were proposed for inclusion in this document. Because the water and concentrates are combined using individual dialysis machines or central dialysis fluid delivery systems that are required to be constructed of materials that do not contribute chemical contaminants to the dialysis fluid, it was concluded that including maximum allowable levels of chemical contaminants in the dialysis fluid would be redundant and impose an unnecessary burden on dialysis facilities.

A.3 Tests for conformity with microbiological requirements

The original clinical observations showing a relationship between bacterial levels in dialysis fluid and pyrogenic reactions were based on cultures performed with standard methods agar (SMA), a medium containing relatively few nutrients[11]. Later, the use of tryptic soy agar (TSA), a general-purpose medium for isolating and cultivating fastidious organisms was recommended because it was thought more appropriate for culturing bicarbonate-containing dialysis fluid.

Recommended methods for assaying fluid microbiological content are shown in Table 1. Such methods provide only a relative indication of the bacterial bioburden rather than an absolute measure. Different media types and incubation periods can result in varying colony concentrations and types of microorganisms recovered[8][46][48].

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[49]. In a more recent publication, 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 above[8].

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[6]. Maltais et al.[8] in their comparison of this medium with TSA also 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 (TGEA and TSA) and their respective 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 on line therapies such as haemodiafiltration. The method selected should be based on the analysis of the advantages, disadvantages and sensitivity of each of the suggested methods. It should also ensure that patient safety is safeguarded, allow for consideration of local laboratory working practices, and that the local regulatory and reimbursement requirements can be met.

The membrane filtration technique is applied when higher sensitivity is required or desired. The use of larger volumes (up to 1 000 ml) will provide greater sensitivity, but the improved sensitivity needs to be balanced against the increased risk of contamination in collecting and handling the sample. Even with the most sensitive techniques, conformity with the stringent requirements for online prepared substitution fluid cannot be demonstrated by culturing, it has to be ensured by use of a validated process.

The presence of non-tuberculous mycobacteria has been associated with several outbreaks of infection in dialysis units[51][52][53].

The recovery of fungi from dialysis fluid implies a potential risk for haemodialysis patients[50]. Currently there are no requirements for routine surveillance for the presence of fungi (i.e. yeasts and filamentous fungi), however if an indication is required, membrane filtration is the preferred method for the obtaining a sample for analysis. The culture media used should be Sabouraud, or Malt Extract Agar (MEA) media. An incubation temperature of 17 °C to 23 °C and an incubation time of 168 h (7 d) are recommended. Other medium, incubation conditions and colony counting times can be used provided it has been demonstrated that such methods have been appropriately validated and are comparable to the cited methods.

Annex B
(informative)

Reference tables

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

Contaminant	Maximum concetraion mg/l[b]
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
Sulphate	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 in charge of dialysis has the ultimate responsibility for ensuring the quality of water used for dialysis.

[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 (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 should not exceed 0,1 mg/l. Since there is no distinction between chlorine and chloramine, this safely assumes that all chlorine present is chloramine.

If verifying disinfectant removal from the dialysis equipment, effluent, free chlorine measurement is acceptable to the limits specified by the manufacturer.

NOTE The maximum allowable levels of contaminants listed in Tables B.1 and B.2 include the anticipated uncertainty associated with the analytical methodologies listed in Table B.3.

Table B.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
NOTE The maximum allowable levels of contaminants listed in Tables B.1 and B.2 include the anticipated uncertainty associated with the analytical methodologies listed in Table B.3.	

Chemical analyses of the substances listed in Tables B.1 and B.2 can be obtained by using methods referenced by ISO, the American Public Health Association, or the US Environmental Protection Agency, or other equivalent analytical methods. Where testing for the individual trace elements listed in Table B.2 is not available, an analysis for total heavy metals can be used with a maximum allowable level of at 0,1 mg/l.

Table B.3 — Analytical test methods for chemical contaminants

Contaminant	Analytical technique	Reference, method number
Aluminium	Inductively coupled plasma mass spectrometry or Atomic Absorption (electrothermal)	ISO 17294–2:2016 American Public Health Assn, #3113
Antimony	Inductively coupled plasma mass spectrometry or Atomic Absorption (platform)	ISO 17294–2:2016 US EPA, #200.9
Arsenic	Inductively coupled plasma mass spectrometry or Atomic Absorption (gaseous hydride)	ISO 17294–2:2016 American Public Health Assn, #3114
Barium	Inductively coupled plasma mass spectrometry or Atomic Absorption (electrothermal)	ISO 17294–2:2016 American Public Health Assn, #3113
Beryllium	Inductively coupled plasma mass spectrometry or Atomic Absorption (platform)	ISO 17294–2:2016 US EPA, #200.9
Cadmium	Inductively coupled plasma mass spectrometry or Atomic Absorption (electrothermal)	ISO 17294–2:2016 American Public Health Assn, #3113
Calcium	Inductively coupled plasma mass spectrometry or EDTA (Ethylene diamine tetra acetic acid) Titrimetric Method, or Atomic Absorption (direct aspiration), or Ion Specific Electrode	ISO 17294–2:2016 American Public Health Assn, #3500-Ca D American Public Health Assn, #3111B
Total chlorine	DPD (N-Diethyl-p-Phenylenediamine)Ferrous Titrimetric Method, or DPD (N-Diethyl-p-Phenylenediamine)Colourimetric Method Thio-Michler's Ketone (TMK/MTK) colourimetric method	American Public Health Assn, #4500-Cl F American Public Health Assn, #4500-Cl G

Table B.3 *(continued)*

Contaminant	Analytical technique	Reference, method number
Chromium	Inductively coupled plasma mass spectrometry or Atomic Absorption (electrothermal)	ISO 17294–2:2016 American Public Health Assn, #3113
Copper	Inductively coupled plasma mass spectrometry or Atomic Absorption (direct aspiration), or Neocuproine Method	ISO 17294–2:2016 American Public Health Assn, #3111 American Public Health Assn, #3500-Cu D
Fluoride	Ion chromatography or Ion Selective Electrode Method, or sodium 2-(parasulfophenylazo)-1,8-dihydroxy-3,6-napthalenedisulfonate (SPADNS) Method	ISO 17294–2:2016 ISO 10359–1:1992 American Public Health Assn, #4500-F- C American Public Health Assn, #4500-F- D
Lead	Inductively coupled plasma mass spectrometry or Atomic Absorption (electrothermal)	ISO 17294–2:2016 American Public Health Assn, #3113
Magnesium	Inductively coupled plasma mass spectrometry or Atomic Absorption (direct aspiration) Ion chromatography	ISO 17294–2:2016 American Public Health Assn, #3111 EPA 300.7:1986
Mercury	Flameless Cold Vapor Technique (Atomic Absorption)	American Public Health Assn, #3112
Nitrate	Ion chromatography or Spectrophotometric method using[sulfosalicylic acid or Cadmium Reduction Method	ISO 10304–1:2007 ISO 7890–3: 2017 American Public Health Assn, #4500-NO_3 E
Potassium	Inductively coupled plasma mass spectrometry or Atomic Absorption (direct aspiration), or Flame Photometric Method, or Ion Specific Electrode	ISO 17294–2:2016 American Public Health Assn, #3111 American Public Health Assn, #3500-K D American Public Health Assn, #3500-K E
Selenium	Inductively coupled plasma mass spectrometry or Atomic Absorption (gaseous hydride), or Atomic Absorption (electrothermal)	ISO 17294–2:2016 American Public Health Assn, #3114 American Public Health Assn, #3113
Silver	Inductively coupled plasma mass spectrometry or Atomic Absorption (electrothermal)	ISO 17294–2:2016 American Public Health Assn, #3113
Sodium	Inductively coupled plasma mass spectrometry or Atomic Absorption (direct aspiration), or Flame Photometric Method, or Ion Specific Electrode	ISO 17294–2:2016 American Public Health Assn, #3111 American Public Health Assn, #3500-Na D
Sulfate	Ion chromatography or Turbidimetric Method	ISO 10304–1:2007 American Public Health Assn, #4500-SO42- E
Thallium	Inductively coupled plasma mass spectrometry or Atomic Absorption (platform)	ISO 17294–2:2016 US EPA, 200.9
Total heavy metals	Colourimetric	European Pharmacopoeia, 2.4.8 US Pharmacopoeia, < 231 >
Zinc	Inductively coupled plasma mass spectrometry or Atomic Absorption (direct aspiration), or Dithizone Method	ISO 17294–2:2016 American Public Health Assn, #3111 American Public Health Assn, #3500-Zn D

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