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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

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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.