BS EN ISO 23500:2015

BSI Standards Publication

Guidance for the preparation and quality management of fluids for haemodialysis and related therapies

bsi.

...making excellence a habit.™

Document Sharing Hub

National foreword

This British Standard is the UK implementation of EN ISO 23500:2015. It is identical to ISO 23500:2014. It supersedes BS ISO 23500:2014 which is withdrawn.

The UK participation in its preparation was entrusted by Technical Committee CH/150, Implants for surgery, to Subcommittee CH/150/2, Cardiovascular implants.

A list of organizations represented on this subcommittee can be obtained on request to its secretary.

This publication does not purport to include all the necessary provisions of a contract. Users are responsible for its correct application.

© The British Standards Institution 2015.
Published by BSI Standards Limited 2015

ISBN 978 0 580 88237 1

ICS 11.040.20; 11.040.40

Compliance with a British Standard cannot confer immunity from legal obligations.

This British Standard was published under the authority of the Standards Policy and Strategy Committee on 31 May 2014.

Amendments/corrigenda issued since publication

Date	Text affected
31 October 2015	This corrigendum renumbers BS ISO 23500:2014 as BS EN ISO 23500:2015

Documents
Document Sharing Hub

Full document details: BS EN ISO 23500:2015

EUROPEAN STANDARD

NORME EUROPÉENNE

EUROPÄISCHE NORM

EN ISO 23500

October 2015

ICS 11.040.40

English Version

Guidance for the preparation and quality management of fluids for haemodialysis and related therapies (ISO 23500:2014)

Directives concernant la préparation et le management de la qualité des fluides d'hémodialyse et de thérapies annexes (ISO 23500:2014)

Leitfaden für die Vorbereitung und das Qualitätsmanagement von Konzentraten für die Hämodialyse und verwandte Therapien (ISO 23500:2014)

This European Standard was approved by CEN on 27 September 2015.

CEN members are bound to comply with the CEN/CENELEC Internal Regulations which stipulate the conditions for giving this European Standard the status of a national standard without any alteration. Up-to-date lists and bibliographical references concerning such national standards may be obtained on application to the CEN-CENELEC Management Centre or to any CEN member.

This European Standard exists in three official versions (English, French, German). A version in any other language made by translation under the responsibility of a CEN member into its own language and notified to the CEN-CENELEC Management Centre has the same status as the official versions.

CEN members are the national standards bodies of Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, Former Yugoslav Republic of Macedonia, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey and United Kingdom.

EUROPEAN COMMITTEE FOR STANDARDIZATION
COMITÉ EUROPÉEN DE NORMALISATION
EUROPÄISCHES KOMITEE FÜR NORMUNG

CEN-CENELEC Management Centre: Avenue Marnix 17, B-1000 Brussels

© 2015 CEN All rights of exploitation in any form and by any means reserved worldwide for CEN national Members.

Ref. No. EN ISO 23500:2015 E

Documents
Document Sharing Hub

Full document details: BS EN ISO 23500:2015

European foreword

The text of ISO 23500:2014 has been prepared by Technical Committee ISO/TC 150 "Implants for surgery" of the International Organization for Standardization (ISO) and has been taken over as EN ISO 23500:2015 by Technical Committee CEN/TC 205 "Non-active medical devices" the secretariat of which is held by DIN.

This European Standard shall be given the status of a national standard, either by publication of an identical text or by endorsement, at the latest by April 2016, and conflicting national standards shall be withdrawn at the latest by April 2016.

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. CEN [and/or CENELEC] shall not be held responsible for identifying any or all such patent rights.

According to the CEN-CENELEC Internal Regulations, the national standards organizations of the following countries are bound to implement this European Standard: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, Former Yugoslav Republic of Macedonia, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey and the United Kingdom.

Endorsement notice

The text of ISO 23500:2014 has been approved by CEN as EN ISO 23500:2015 without any modification.

Documents
Document Sharing Hub

Full document details: BS EN ISO 23500:2015

Contents

Page

Foreword ... **iv**

Introduction ... **v**

1 Scope ... **1**
1.1 General ... 1
1.2 Inclusions ... 1
1.3 Exclusions ... 1

2 Normative references ... **1**

3 Terms and definitions ... **2**

4 Summary of quality requirements of ISO 13958, ISO 13959 and ISO 11663 ... **9**
4.1 Dialysis water ... 9
4.2 Requirements for concentrate ... 11
4.3 Requirements for dialysis fluid ... 11
4.4 Record retention ... 12

5 Critical aspects of system design ... **12**
5.1 Technical aspects ... 13
5.2 Microbiological aspects ... 13

6 Validation of system performance ... **14**
6.1 Validation plan ... 14
6.2 Installation and operational qualification ... 15
6.3 Performance qualification ... 16
6.4 Routine monitoring and revalidation ... 16

7 Quality management ... **17**
7.1 General ... 17
7.2 Monitoring of fluid quality ... 17
7.3 Monitoring of water treatment equipment ... 18
7.4 Monitoring of dialysis water storage and distribution ... 21
7.5 Monitoring of concentrate preparation ... 23
7.6 Monitoring of concentrate distribution ... 23
7.7 Monitoring of dialysis fluid proportioning ... 23

8 Strategies for microbiological control ... **24**
8.1 General ... 24
8.2 Disinfection ... 24
8.3 Microbiological monitoring methods ... 26

9 Environment ... **28**

10 Personnel ... **29**

Annex A (informative) **Rationale for the development and provisions of this International Standard** ... **30**

Annex B (informative) **Equipment** ... **34**

Annex C (informative) **Monitoring guidelines for water treatment equipment, distribution systems, and dialysis fluid** ... **52**

Annex D (informative) **Strategies for microbiological control** ... **57**

Annex E (informative) **Validation** ... **62**

Annex F (informative) **Special considerations for home haemodialysis** ... **65**

Annex G (informative) **Special considerations for acute haemodialysis** ... **71**

Bibliography ... **76**

Documents
Document Sharing Hub

© ISO 2014 – All rights reserved

Full document details: BS EN ISO 23500:2015

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 on the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the WTO principles in the Technical Barriers to Trade (TBT) see the following URL: Foreword - Supplementary information

The committee responsible for this document is ISO/TC 150, *Implants for surgery*, Subcommittee SC 2, *Cardiovascular implants and extracorporeal systems*.

This second edition cancels and replaces the first edition (ISO 23500:2011), which has been technically revised.

© ISO 2014 – All rights reserved
Documents
Document Sharing Hub
Full document details: BS EN ISO 23500:2015

Introduction

This International Standard was developed by ISO/TC 150/SC 2. The objective was to provide users with guidance for handling water and concentrates and for the production and monitoring of dialysis fluid used for haemodialysis. The need for such guidance is based on the critical role of dialysis fluid quality in providing safe and effective haemodialysis, and the recognition that day-to-day dialysis fluid quality is under the control of the healthcare professionals who deliver dialysis therapy.

Quality requirements for the water and concentrates used to prepare dialysis fluid, and for that dialysis fluid, are provided in ISO 13959, ISO 13958, and ISO 11663, respectively. This International Standard does not address clinical issues that might be associated with inappropriate usage of the water, dialysis water, concentrates, or dialysis fluid. Healthcare professionals involved in the provision of treatment for kidney failure should make the final decision regarding the applications with which these fluids are used, for example, haemodialysis, haemodiafiltration, high-flux haemodialysis, and the reprocessing of dialysers, and need to be aware of the issues that the use of inappropriate fluid quality raises in each of the therapies.

The equipment used in the various stages of dialysis fluid preparation is generally obtained from specialized vendors. Dialysis practitioners are generally responsible for maintaining that equipment following its installation. Therefore, this International Standard provides guidance on monitoring and maintenance of the equipment to ensure that dialysis fluid quality is acceptable at all times. At various places throughout this International Standard, the user is advised to follow the manufacturer's instructions regarding the operation and maintenance of equipment. In those instances in which the equipment is not obtained from a specialized vendor, it is the responsibility of the user to validate the performance of the equipment in the haemodialysis setting and to ensure that appropriate operating and maintenance manuals are available. Annex B provides a general description of the system components that are used for water treatment, concentrate, and dialysis fluid preparation at a dialysis facility. These descriptions are intended to provide the user with a basis for understanding why certain equipment might be required and how it should be configured; they are not intended as detailed design standards. Requirements for water treatment equipment are provided in ISO 26722.

The verbal forms used in this International Standard conform to usage described in Annex H of the ISO/IEC Directives, Part 2:2004. For the purposes of this International standard, the auxiliary verb:

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

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

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

This International Standard reflects the conscientious efforts of healthcare professionals, patients, and medical device manufacturers to develop recommendations for handling water and concentrates and for the production and monitoring of dialysis fluid for haemodialysis. This International Standard is directed towards the healthcare professionals involved in the management or routine care of haemodialysis patients and responsible for the quality of dialysis fluid. The recommendations contained in this International Standard might not be applicable in all circumstances and they are not intended for regulatory application.

The guidance provided by this International Standard should help protect haemodialysis patients from adverse effects arising from known chemical and microbial contaminants that might 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 requirements of all applicable quality standards.

The concepts incorporated in this International Standard should not be considered inflexible or static. The 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.

AVA Documents
Document Sharing Hub

© ISO 2014 – All rights reserved

Full document details: BS EN ISO 23500:2015

Documents
Document Sharing Hub

INTERNATIONAL STANDARD

Guidance for the preparation and quality management of fluids for haemodialysis and related therapies

1 Scope

1.1 General

This International Standard provides dialysis practitioners with guidance on the preparation of dialysis fluid for haemodialysis and related therapies and substitution fluid for use in online therapies, such as haemodiafiltration and haemofiltration. As such, this International Standard functions as a recommended practice.

1.2 Inclusions

This International Standard addresses the user's responsibility for the dialysis fluid once the equipment used in its preparation has been delivered and installed. For the purposes of this International Standard, the dialysis fluid includes dialysis water (see 3.18 for definition) used for the preparation of dialysis fluid and substitution fluid, dialysis water used for the preparation of concentrates at the user's facility, as well as concentrates and the final dialysis fluid and substitution fluid.

The scope of this International Standard includes

a) the quality management of equipment used to treat and distribute water used for the preparation of dialysis fluid and substitution fluid, from the point at which municipal water enters the dialysis facility to the point at which the final dialysis fluid enters the dialyser or the point at which substitution fluid is infused,

b) equipment used to prepare concentrate from powder or other highly concentrated media at a dialysis facility, and

c) preparation of the final dialysis fluid or substitution fluid from dialysis water and concentrates.

NOTE Because water used to prepare dialysis fluid is commonly prepared and distributed using the same equipment as the water used to reprocess dialysers, water used to reprocess dialysers is also covered by this International Standard.

1.3 Exclusions

This International Standard does not apply to sorbent-based dialysis fluid regeneration systems that regenerate and recirculate small volumes of dialysis fluid, systems for continuous renal replacement therapy that use prepackaged solutions, and systems and solutions for peritoneal dialysis.

2 Normative references

The following documents, in whole or in part, are normatively referenced in this document and are indispensable for its application. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 11663:2014, *Quality of dialysis fluid for haemodialysis and related therapies*

ISO 13958:2014, *Concentrates for haemodialysis and related therapies*

ISO 13959:2014, *Water for haemodialysis and related therapies*

© ISO 2014 – All rights reserved

Documents
Document Sharing Hub
Full document details: BS EN ISO 23500:2015

ISO 26722:2014, *Water treatment equipment for haemodialysis applications and related therapies*

3 Terms and definitions

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

3.1
acetate concentrate
concentrated solution of salts containing acetate, which, when diluted with dialysis water, yields bicarbonate-free dialysis fluid for use in dialysis

Note 1 to entry: Acetate concentrate may contain glucose.

Note 2 to entry: Sodium acetate is used to provide buffer in place of sodium bicarbonate.

Note 3 to entry: Acetate concentrate is used as a single concentrate.

3.2
acid concentrate
A-concentrate
acidified concentrated mixture of salts that, when diluted with dialysis water and bicarbonate concentrate, yields dialysis fluid for use in dialysis

Note 1 to entry: The term "acid" refers to the small amount of acid (for example, acetic acid or citric acid) that is included in the concentrate.

Note 2 to entry: Acid concentrate may contain glucose.

Note 3 to entry: Acid concentrate may be in the form of a liquid, a dry powder, other highly concentrated media, or some combination of these forms.

3.3
action level
concentration of a contaminant at which steps should be taken to interrupt the trend toward higher, unacceptable levels

3.4
additive
spike
small amount of a single chemical that, when added to the concentrate, will increase the concentration of a single existing chemical by a value labelled on the additive packaging

3.5
bicarbonate concentrate
B-concentrate
concentrated preparation of sodium bicarbonate that, when diluted with dialysis water and acid concentrate, makes dialysis fluid used for dialysis

Note 1 to entry: Sodium bicarbonate is also known as sodium hydrogen carbonate.

Note 2 to entry: Some bicarbonate concentrates also contain sodium chloride.

Note 3 to entry: Bicarbonate concentrate may be in the form of a liquid or a dry powder.

Note 4 to entry: Dry sodium bicarbonate, without added sodium chloride, is also used in concentrate generators to produce a concentrated solution of sodium bicarbonate used by the dialysis machine to make dialysis fluid.

© ISO 2014 – All rights reserved
Documents
Document Sharing Hub
Full document details: BS EN ISO 23500:2015

3.6
biofilm
microbially-derived sessile community characterized by cells that are irreversibly attached to a substratum or interface or to each other, are imbedded in a matrix of extracellular polymeric substances that they have produced, and exhibit an altered phenotype with respect to growth rate and gene transcription

Note 1 to entry: The matrix, a slimy material secreted by the cells, protects the bacteria from antibiotics and chemical disinfectants.

Note 2 to entry: A certain amount of biofilm formation is considered unavoidable in dialysis water systems. When the level of biofilm is such that the action levels for microorganisms and endotoxins in the dialysis water cannot be routinely achieved, the operation of the system is compromised from a medical and technical point of view. This level of biofilm formation is often referred to as biofouling.

3.7
bulk delivery
delivery of large containers of concentrate to a dialysis facility

Note 1 to entry: Bulk delivery includes containers such as drums, which can be pumped into a storage tank maintained at the user's facility. Alternatively, the drums can be left at the facility and used to fill transfer containers to transfer the concentrate to the dialysis machines. Bulk delivery can also include large containers for direct connection to a central concentrate supply system.

Note 2 to entry: Bulk delivery also includes dry powder concentrates intended to be used with an appropriate concentrate mixer.

3.8
central concentrate system
system that prepares and/or stores concentrate at a central point for subsequent distribution to its points of use

3.9
central dialysis fluid delivery system
system that produces dialysis fluid from dialysis water and concentrate or powder at a central point and distributes the dialysis fluid from the central point to individual dialysis machines

3.10
chlorine, combined
chlorine that is chemically combined, such as in chloramine compounds

Note 1 to entry: There is no direct test for measuring combined chlorine, but it can be measured indirectly by measuring both total and free chlorine and calculating the difference.

3.11
chlorine, free
chlorine present in water as dissolved molecular chlorine (Cl), hypochlorous acid (HOCl), and hypochlorite ion (OCl^-)

Note 1 to entry: The three forms of free chlorine exist in equilibrium.

3.12
chlorine, total
sum of free and combined chlorine

Note 1 to entry: Chlorine can exist in water as dissolved molecular chlorine, hypochlorous acid, and/or hypochlorite ion (free chlorine) or in chemically combined forms (combined chlorine). Where chloramine is used to disinfect water supplies, chloramine is usually the principal component of combined chlorine.

© ISO 2014 – All rights reserved

Documents
Document Sharing Hub
Full document details: BS EN ISO 23500:2015

3.13
colony-forming unit
CFU
measure of bacterial or fungal cell numbers that theoretically arise from a single cell when grown on solid media

Note 1 to entry: Colonies can also form from groups of organisms when they occur in aggregates.

3.14
concentrate generator
system where the concentrate is delivered to the user as a powder in a container, suitable for attachment to the dialysis machine with which it is intended to be used, and then the powder is converted into a concentrated solution by the dialysis machine

Note 1 to entry: The solution produced by the concentrate generator is used by the dialysis machine to make the final dialysis fluid delivered to the dialyser.

3.15
device
individual dialysis water purification unit, such as a softener, carbon bed, reverse osmosis unit, or deionizer

Note 1 to entry: This term is synonymous with the term "component" as used by the US Food and Drug Administration (see Reference[169]).

3.16
dialysis fluid
dialysate
dialysis solution
aqueous fluid containing electrolytes and, usually, buffer and glucose, which is intended to exchange solutes with blood during haemodialysis

Note 1 to entry: The term "dialysis fluid" is used throughout this International Standard to mean the fluid made from dialysis water and concentrates that is delivered to the dialyser by the dialysis fluid delivery system. Such phrases as "dialysate" or "dialysis solution" are used in place of dialysis fluid in some countries; however, that usage is discouraged to avoid confusion.

Note 2 to entry: The dialysis fluid entering the dialyser is referred to as "fresh dialysis fluid", while the fluid leaving the dialyser is referred to as "spent dialysis fluid".

Note 3 to entry: Dialysis fluid does not include prepackaged parenteral fluids used in some renal replacement therapies, such as haemodiafiltration and haemofiltration.

3.17
dialysis fluid delivery system
device that prepares dialysis fluid online from dialysis water and concentrates or that stores and distributes premixed dialysis fluid; circulates the dialysis fluid through the dialyser; monitors the dialysis fluid for temperature, conductivity (or equivalent), pressure, flow, and blood leaks; and, prevents dialysis during disinfection or cleaning modes

Note 1 to entry: The term includes reservoirs, conduits, proportioning devices for the dialysis fluid, and monitors and associated alarms and controls assembled as a system for the purposes listed above.

Note 2 to entry: The dialysis fluid delivery system may be an integral part of the single-patient dialysis machine or a centralized preparation system which feeds multiple bedside monitoring systems.

Note 3 to entry: Dialysis fluid delivery systems are also known as proportioning systems and dialysis fluid supply systems.

© ISO 2014 – All rights reserved
Documents
Document Sharing Hub
Full document details: BS EN ISO 23500:2015

3.18
dialysis water
water that has been treated to meet the requirements of ISO 13959 and which is suitable for use in haemodialysis applications, including the preparation of dialysis fluid, reprocessing of dialysers, preparation of concentrates and preparation of substitution fluid for online convective therapies

3.19
disinfection
destruction of pathogenic and other kinds of microorganisms by thermal or chemical means

Note 1 to entry: Disinfection is a less lethal process than sterilization because it destroys most recognized pathogenic microorganisms but does not necessarily destroy all microbial forms.

3.20
empty-bed contact time
EBCT
time taken by a fluid to pass through an empty volume equal to the volume of a particle bed

Note 1 to entry: EBCT (min) is calculated from the following formula:

$$\text{EBCT} = V/Q$$

where

V is the volume of the particle bed, in cubic metres (m^3);

Q is the flow rate of water through the bed, in cubic metres per minute (m^3/min).

Note 2 to entry: EBCT is used as an indirect measure of how much contact occurs between particles, such as activated carbon, and water as the water flows through a bed of particles.

3.21
endotoxin
major component of the outer cell wall of gram-negative bacteria

Note 1 to entry: Endotoxins are lipopolysaccharides, which consist of a polysaccharide chain covalently bound to lipid A. Endotoxins can acutely activate both humoral and cellular host defences, leading to a syndrome characterized by fever, shaking, chills, hypotension, multiple organ failure, and even death if allowed to enter the circulation in a sufficient dose. [See also *pyrogen* (3.36)].

3.22
endotoxin-retentive filter
ETRF
membrane filter used to remove endotoxins and microorganisms from dialysis water or dialysis fluid

Note 1 to entry: The performance of an endotoxin-retentive filter is usually expressed as the logarithmic reduction value (LRV), defined as $\log_{10}$(inlet concentration)/(outlet concentration).

Note 2 to entry: Endotoxin-retentive filters may be configured in a cross-flow or dead-end mode. Some endotoxin-retentive filters also remove endotoxins by adsorption.

3.23
endotoxin units
EU
units assayed by the *Limulus* amoebocyte lysate (LAL) test when testing for endotoxins

Note 1 to entry: Because activity of endotoxins depends on the bacteria from which they are derived, their activity is referred to a standard endotoxin.

Note 2 to entry: In some countries, endotoxin concentrations are expressed in international units (IU). Since the harmonization of endotoxin assays, EU and IU are equivalent.

© ISO 2014 – All rights reserved

Documents
Document Sharing Hub
Full document details: BS EN ISO 23500:2015

3.24
feed water
water supplied to a water treatment system or to an individual component of a water treatment system

3.25
germicide
agent that kills microorganisms

3.26
haemodiafiltration
form of renal replacement therapy in which waste solutes are removed from blood by a combination of diffusion and convection through a high-flux membrane

Note 1 to entry: Diffusive solute removal is achieved using a dialysis fluid stream as in haemodialysis. Convective solute removal is achieved by adding ultrafiltration in excess of that needed to obtain the desired weight loss; fluid balance is maintained by infusing a replacement solution into the blood either before the dialyser (predilution haemodiafiltration), after the dialyser (postdilution haemodiafiltration), or a combination of the two (mixed dilution haemodiafiltration).

3.27
haemodialysis
form of renal replacement therapy in which waste solutes are removed primarily by diffusion from blood flowing on one side of a membrane into dialysis fluid flowing on the other side

Note 1 to entry: Fluid removal that is sufficient to obtain the desired weight loss is achieved by establishing a hydrostatic pressure gradient across the membrane. This fluid removal provides some additional waste solute removal, particularly for solutes with higher molecular weight.

3.28
haemofiltration
form of renal replacement therapy in which waste solutes are removed from blood by convection

Note 1 to entry: Convective transport is achieved by ultrafiltration through a high-flux membrane. Fluid balance is maintained by infusing a replacement solution into the blood either before the haemofilter (predilution haemofiltration), after the haemofilter (postdilution haemofiltration), or a combination of the two (mixed dilution haemofiltration).

Note 2 to entry: There is no dialysis fluid stream in haemofiltration.

3.29
heterotrophic
not self-sustaining, i.e. a type of nutrition in which organisms derive energy from the oxidation of organic compounds by either consumption or absorption of other organisms

3.30
***Limulus* amoebocyte lysate test**
LAL test
assay used to detect endotoxin

Note 1 to entry: The detection method uses the chemical response of an extract from blood cells of a horseshoe crab (*Limulus polyphemus*) to endotoxins.

Note 2 to entry: Amebocyte lysate from a second horseshoe crab, *Tachypleus tridentatus*, may also be used to detect endotoxin.

© ISO 2014 – All rights reserved
Documents
Document Sharing Hub
Full document details: BS EN ISO 23500:2015

3.31
manufacturer
entity that designs, manufactures, fabricates, assembles, or processes a finished device

Note 1 to entry: Manufacturers include, but are not limited to, those who perform the functions of contract sterilization, installation, relabelling, remanufacturing, repacking, or specification development, and initial distributions of foreign entities performing these functions. The term does not cover preparation of concentrates from prepackaged dry chemicals at a dialysis facility or the handling of bulk concentrates at a dialysis facility after responsibility for the concentrate is transferred from the manufacturer to the user.

3.32
microbiological contamination
contamination with any form of microorganism (e.g. bacteria, yeast, fungi, and algae) or with the by-products of living or dead organisms, such as endotoxins, exotoxins, and cyanobacterial toxins (derived from blue-green algae)

3.33
nonpyrogenic
not eliciting a pyrogen reaction

Note 1 to entry: Historically, the threshold pyrogenic dose of 5 EU/kg/h (the minimum dose that produces fever) has been used to set endotoxin limits of devices and injectable medications.

Note 2 to entry: The volume of fluid administered should not exceed the volume that would result in a total dose of endotoxin of ≥5 EU/kg/h.

Note 3 to entry: This definition is applicable for fluids produced by online techniques, e.g. substitution and priming fluids.

Note 4 to entry: The commonly used gel clot method has a sensitivity limit of 0,03 EU/ml.

3.34
product water
water produced by a water treatment system or by an individual device thereof

3.35
proportioning system
apparatus that proportions dialysis water and haemodialysis concentrate to prepare dialysis fluid

3.36
pyrogen
fever-producing substance

Note 1 to entry: Pyrogens are most often lipopolysaccharides of gram-negative bacterial origin [see also *endotoxin* (3.21)].

3.37
sodium hypochorite
chemical used for disinfection of haemodialysis systems

Note 1 to entry: Commercially available solutions of sodium hypochlorite are known in different countries by terms such as bleach and javel. These solutions are used for disinfection at concentrations recommended by equipment manufacturers.

3.38
source water
water entering a dialysis facility from an external supplier, such as a municipal water supply

Note 1 to entry: Source water is sometimes referred to as feed water.

© ISO 2014 – All rights reserved

Documents
Document Sharing Hub
Full document details: BS EN ISO 23500:2015

3.39
sterile
free from viable microorganisms

Note 1 to entry: "Sterile" can be used to describe a packaged solution that was prepared using a terminal sterilization process validated according to the methods of the applicable pharmacopoeia. A terminal sterilization process is commonly defined as one that achieves a sterility assurance level (SAL) of 10^{-6}, i.e. assurance of less than one chance in a million that viable microorganisms are present in the sterilized article.

Note 2 to entry: Alternatively, "sterile" can be used to describe a solution prepared for immediate use by a continuous process, such as filtration, that has been validated according to the methods of the applicable pharmacopoeia to produce a solution free from microorganisms for the validated life of the filter.

3.40
storage tank
tank at the user's facility for storage of dialysis water or concentrate from bulk deliveries, or for concentrate prepared in bulk at the user's facility from powder and dialysis water

3.41
substitution fluid
fluid used in haemofiltration and haemodiafiltration treatments which is infused directly into the patient's blood as a replacement for the fluid that is removed from the blood by filtration

Note 1 to entry: Substitution fluid is also referred to as substitution solution or replacement solution.

Note 2 to entry: Substitution fluid can also be used for bolus administration, for priming of an extracorporeal blood circuit, and for returning blood to the patient at the end of a treatment.

3.42
total dissolved solids
TDS
sum of all ions in a solution, often approximated by means of electrical conductivity or resistivity measurements

Note 1 to entry: TDS measurements are commonly used to assess the performance of reverse osmosis units. TDS values are often expressed in terms of $CaCO_3$, NaCl, KCl, or 442 equivalents, in milligrams per litre (mg/l). [442 is a solution of sodium sulfate (40 %), sodium bicarbonate (40 %), and sodium chloride (20 %) that closely represents the conductivity to concentration relationship, on average, for naturally occurring fresh water.]

3.43
ultrapure dialysis fluid
highly purified dialysis fluid that can be used in place of conventional dialysis fluid

Note 1 to entry: A widely accepted specification of ultrapure dialysis fluid is <0,1 CFU/ml and <0,03 EU/ml.

3.44
user
physician or physician's representative or healthcare professional with a responsibility for the prescription, production, and delivery of dialysis fluid

3.45
validation
process of documenting that the dialysis water treatment and dialysis fluid production systems, when installed and operated according to the manufacturer's recommendations, consistently produce dialysis water or dialysis fluid meeting the stipulated quality levels

Note 1 to entry: In this context, validation also includes demonstrating that the system is "fit for purpose".

Note 2 to entry: The term "verification" is also used and refers to demonstrating that the system complies with applicable regulations, specifications, or other conditions. A dialysis facility might be interested in both validation and verification of its fluid production systems.

© ISO 2014 – All rights reserved
Documents
Document Sharing Hub
Full document details: BS EN ISO 23500:2015

3.46
water treatment system
collection of water treatment devices and associated piping, pumps, valves, gauges, etc., that together produce water for dialysis meeting the requirements of ISO 13959 for haemodialysis applications and deliver it to the point of use

4 Summary of quality requirements of ISO 13958, ISO 13959 and ISO 11663

The quality requirements set forth in this clause are reproduced from the 2014 editions of ISO 13958, ISO 13959, and ISO 11663. The latest editions of these International Standards should be consulted to ascertain if there have been any changes to those requirements before implementing the recommendations of this International Standard.

4.1 Dialysis water

4.1.1 General

The requirements contained in this clause apply to dialysis water at its point of use. As such, these requirements apply to the water treatment system as a whole and not to each of the devices that make up the system. However, collectively, the individual devices shall produce water that, at a minimum, meets the requirements of this clause.

4.1.2 Chemical contaminants in dialysis water

Dialysis water shall not contain substances at levels greater than those listed in ISO 13959 (see Tables 1 and 2). The manufacturer or supplier of a complete water treatment system should recommend a system that is capable of meeting these requirements based on a feed water analysis. The system design should reflect possible seasonal variations in feed-water quality. The manufacturer or supplier of a complete water treatment and distribution system should demonstrate that the complete water treatment, storage, and distribution system is capable of meeting the requirements of ISO 13959 at the time of installation.

NOTE The maximum allowable levels of contaminants listed in Tables 1 and 2 include the anticipated uncertainty associated with the analytical methodologies listed in Table 3 of ISO 13959. Other analytical methods can be used, provided that such methods have been appropriately validated and compared to the cited methods.

Following installation of a water treatment, storage, and distribution system, the user is responsible for regular monitoring of the levels of chemical contaminants in the dialysis water and for complying with the requirements of this International Standard.

Tables 1 and 2 are reproduced from ISO 13959:2014.

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

Contaminant	Maximum concentration (mg/l)[c]
Contaminants with documented toxicity in haemodialysis	
Aluminium	0,01
Total chlorine	0,1
Copper	0,1

[a] A dialysis facility's Medical Director has the ultimate responsibility for ensuring the quality of dialysis water.

[b] The reader is cautioned to refer to the latest version of ISO 13959 to ensure that there have been no changes to this table.

[c] Unless otherwise noted.

© ISO 2014 – All rights reserved

Documents
Document Sharing Hub
Full document details: BS EN ISO 23500:2015

Table 1 *(continued)*

Contaminant	Maximum concentration (mg/l)[c]
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 dialysis facility's Medical Director has the ultimate responsibility for ensuring the quality of dialysis water.

[b] The reader is cautioned to refer to the latest version of ISO 13959 to ensure that there have been no changes to this table.

[c] Unless otherwise noted.

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

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

[a] The reader is cautioned to refer to the latest version of ISO 13959 to ensure that no changes have been made to the maximum concentrations shown.

4.1.3 Microbiological contaminants in dialysis water

The total viable microbial count and endotoxin concentration in dialysis water shall comply with the maximum allowable levels specified in ISO 13959 (see Table 3). Action levels for the total viable microbial count and endotoxin concentration shall also be set, based on knowledge of the microbial dynamics of the system. Typically, the action level is set at 50 % of the maximum allowable level for bacteria and endotoxins. If a total viable microbial count or endotoxin concentration at or above the action level is observed in the dialysis water, corrective measures should be taken promptly to reduce the level. The manufacturer or supplier of a complete water treatment and distribution system should demonstrate that the complete water treatment, storage, and distribution system is capable of meeting the requirements of ISO 13959 at the time of installation.

Following installation of a water treatment, storage and distribution system, the user is responsible for regular monitoring of the microbiology of the system and for complying with the requirements of this International Standard, including those requirements related to action levels.

© ISO 2014 – All rights reserved
Documents
Document Sharing Hub
Full document details: BS EN ISO 23500:2015

Table 3 is adapted from ISO 13959:2014.

Table 3 — Maximum allowable levels for total viable microbial count (TVC) and endotoxins in dialysis water[a]

Contaminant	Maximum allowable level	Typical action level[b]
TVC	<100 CFU/ml	50 CFU/ml
Endotoxin	<0,25 EU/ml	0,125 EU/ml

[a] The reader is cautioned to refer to the latest version of ISO 13959 to ensure that there have been no changes to the values presented in this table.

[b] Typically set at 50 % of the maximum allowable level. Other values may be set.

4.2 Requirements for concentrate

4.2.1 Chemical and microbiological contaminants in concentrate

Concentrates used to prepare dialysis fluid shall comply with the quality requirements specified in ISO 13958.

Bicarbonate concentrate can grow bacteria and caution should be used to limit the bacterial levels in bicarbonate concentrate.

4.2.2 Water used to prepare concentrate

Water used to prepare concentrates at a dialysis facility shall meet the requirements of ISO 13959. Any concentrate prepared at a dialysis facility shall permit the dialysis machine to prepare dialysis fluid meeting the requirements of ISO 11663.

4.3 Requirements for dialysis fluid

4.3.1 General

The requirements contained in this clause apply to a sample of the dialysis fluid collected as close as practicable to the inlet to the dialyser.

ISO 11663 defines three levels of dialysis fluid: standard dialysis fluid, ultrapure dialysis fluid, and online-prepared substitution fluid. Standard dialysis fluid is considered the minimum acceptable quality for routine haemodialysis. Ultrapure dialysis fluid is recommended for routine haemodialysis.

4.3.2 Microbiological requirements for standard dialysis fluid

The total viable microbial count and endotoxin concentration in standard dialysis fluid shall comply with the maximum allowable levels specified in ISO 11663 and reproduced in Table 4. Action levels for the total viable microbial count and endotoxin concentration shall also be set, based on knowledge of the microbial dynamics of the system as specified in ISO 11663. Typically, the action level is set at 50 % of the maximum allowable level for total viable microbial count and endotoxins. If total viable microbial counts or endotoxin concentrations at or above the action levels are observed in the dialysis fluid, corrective measures, such as disinfection and retesting, should promptly be taken to reduce the levels.

Table 4 is adapted from ISO 11663:2014.

© ISO 2014 – All rights reserved

Documents
Document Sharing Hub
Full document details: BS EN ISO 23500:2015

Table 4 — Maximum allowable levels for total viable microbial count (TVC) and endotoxins in standard and ultrapure dialysis fluid[a]

Contaminant	Standard dialysis fluid		Ultrapure dialysis fluid
	Maximum allowable level	Action level[b]	Maximum allowable level
TVC	<100 CFU/ml	50 CFU/ml	<0,1 CFU/ml
Endotoxin	<0,5 EU/ml	0,25 EU/ml	<0,03 EU/ml

[a] The reader is cautioned to refer to the latest version of ISO 11663 to ensure that there have been no changes to this table.

[b] Typically set at 50 % of the maximum allowable level. Other values may be set.

4.3.3 Microbiological requirements for ultrapure dialysis fluid

The total viable microbial count and endotoxin concentration in ultrapure dialysis fluid shall comply with the maximum allowable levels specified in ISO 11663 and reproduced in Table 4. If those limits are exceeded in ultrapure dialysis fluid, corrective measures should be taken to reduce the levels into an acceptable range. The user is responsible for monitoring the dialysis fluid bacteriology of the system following installation.

NOTE Tests for bacterial growth and endotoxins are not required if the system is fitted with an endotoxin-retentive filter validated by the manufacturer and operated and monitored according to the manufacturer's instructions, unless the manufacturer requires those tests in the instructions for use.

4.3.4 Microbiological requirements for online-prepared substitution fluid

The recommendations contained in this clause apply to substitution fluid as it enters the patient's blood.

This fluid shall be sterile and nonpyrogenic according to the recommendations of ISO 11663.

Substitution fluid for convective therapies, such as haemodiafiltration and haemofiltration, or for priming the extracorporeal circuit or bolus administration of fluid during a treatment, may be produced online by a process of ultrafiltration with endotoxin-retentive filters. This online process shall be validated by the manufacturer to produce substitution fluid that is sterile and nonpyrogenic.

The user should follow the manufacturer's instructions for the installation, use, maintenance, and monitoring of the validated system. The function of the validated system should be verified according to the manufacturer's instructions at the time of installation and confirmed by the user with regular monitoring. Monitoring shall include confirmation that the dialysis water and concentrates used by the validated system to prepare the substitution fluid continue to meet the specifications of ISO 13958 and ISO 13959.

4.4 Record retention

Records of installation, monitoring, maintenance, and disinfection of the water treatment and dialysis fluid preparation systems, medical observation, and personnel education shall be kept according to national regulations. In the absence of national regulations, it is recommended that these records should be retained for the same period as clinical records.

5 Critical aspects of system design

The preparation of dialysis fluid, from inlet municipal water and acquisition of concentrates to discharge of spent dialysis fluid into the drain system, involves numerous components that, together, form a dialysis fluid handling system. The technical features of the water treatment component of that system should be based on the criteria listed in ISO 26722, with special regard to the aspects related to the dialysis water quality, the optimal use of resources (e.g. water and energy), and the operations of disinfection and maintenance. Concentrates may be obtained from a supplier in a ready-to-use form or prepared at the dialysis facility from dialysis water and prepackaged salts. The technical features of

© ISO 2014 – All rights reserved
AVA Documents Document Sharing Hub
Full document details: BS EN ISO 23500:2015

the concentrate preparation and distribution component of the system should be based on the criteria listed in ISO 13958.

5.1 Technical aspects

In accordance with the requirements listed in ISO 26722, the system design should specifically address the following points:

— compliance with mandatory local regulations;

— capability to operate with the available feed-water supply and over the anticipated range of variation in the quality of that water, to include both variations arising from changes in the quality of the source water used by the provider of the feed water and variations introduced by the provider in treating that water;

NOTE Source water is assumed to be potable water.

— provision for adequate process monitoring;

— service and maintenance.

If the entire fluid handling system is not obtained from a single supplier, then the user becomes responsible for ensuring that the separate parts of the system are compatible. For example, it is important that the pretreatment section of the water treatment system be designed to supply the main purification device (usually reverse osmosis) with feed water meeting the specifications for that device, i.e. pressure, temperature, flow, and quality (for example, elimination of chemicals which cannot be effectively removed by the main purification device or that could damage it).

The choice of the water treatment system should consider the following aspects concerning the feed-water supply:

— full chemical analysis of the feed water and silt density index (SDI);

— microbiological load, which could lead to the introduction of an additional chlorination step;

— flow rates, pressure, and temperature;

— the treatment techniques used by the provider of the feed water (for example, addition of chloramine, fluoride, aluminium sulfate, etc.). Because treatment techniques can change, ongoing communication with the provider of the feed water is recommended.

5.2 Microbiological aspects

The required microbiological quality of the dialysis water and dialysis fluid is achieved by paying adequate attention to the entire water treatment and dialysis fluid preparation cascade. For this reason, the system should be designed to reduce, as much as possible, potential sources of contamination and to allow effective monitoring and disinfection of the critical parts.

When applicable, equipment should be operated on a regular basis to reduce stagnation.

The distribution system should be designed to maintain dialysis water or dialysis fluid quality and, therefore, should fulfil the following criteria:

— the distribution loop should be of the minimum length, and avoid multiple branches and dead ends;

— materials shall be compatible with the different operational conditions (i.e. supply, disinfection, cleaning);

— there should be no release of chemicals and nutrients for microorganisms;

— temperature increases or exposure to sunlight should be minimized.

© ISO 2014 – All rights reserved

Documents
Document Sharing Hub
Full document details: BS EN ISO 23500:2015

Suitable sampling ports should be available at the start and the end of the distribution loop.

6 Validation of system performance

The validation process should provide documentary evidence that the system will consistently produce dialysis water, dialysis fluid, or substitution fluid meeting the quality requirements of ISO 13959 or ISO 11663. An example of the validation process is presented schematically in Figure 1.

NOTE The rationale for the validation process is given in Annex E.

The validation process consists of the following:

— assignment of operational responsibility;

— assignment of clinical responsibility;

— assignment of legal responsibility;

— validation plan;

— installation and operational qualification;

— performance qualification;

— revalidation as it relates to routine monitoring.

6.1 Validation plan

The validation plan should be a clear and concise document covering the following:

— description of relevant systems, equipment, or processes;

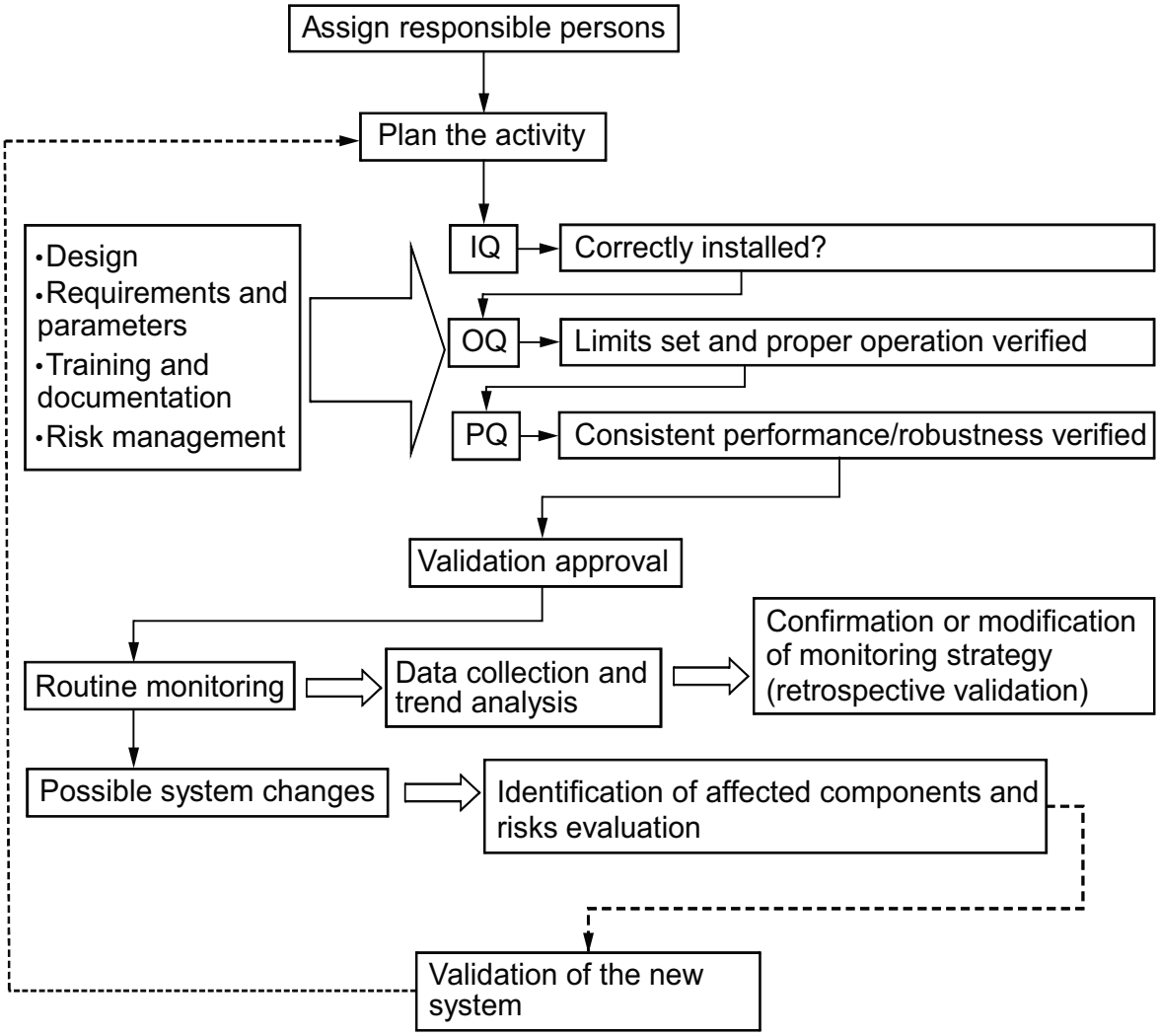
— current status of those systems, equipment, or processes;

— procedures for making changes to systems, equipment, or processes;

— planning and scheduling, including the addition of new systems, activities driven by change, and periodic review.

The validation plan should be approved by the person at the dialysis facility with overall responsibility for dialysis fluids.

© ISO 2014 – All rights reserved
Documents
Document Sharing Hub
Full document details: BS EN ISO 23500:2015



Key

IQ installation qualification

OQ operational qualification

PQ performance qualification

Figure 1 — Example of a validation process for a fluid preparation and distribution system

6.2 Installation and operational qualification

The installation qualification defines and provides the documented proof that the system is installed in accordance with the approved plans and the manufacturer's technical requirements and specifications. Full system documentation should be available on completion of this procedure, including system flow diagrams and layout, log books, and operator's manuals. The installation should be carried out by qualified personnel in line with the manufacturer's recommendations.

The installation qualification should be followed by an operational qualification that verifies the proper operation of the system, including range of operation, set point and interlock testing, and functional testing, and that compares the system performance with the functional specifications of the system. On completion of this phase, the following information should be available:

— test records;

— set-up record;

© ISO 2014 – All rights reserved

Documents
Document Sharing Hub
Full document details: BS EN ISO 23500:2015

— calibration schedule;

— sampling procedures;

— maintenance (e.g. disinfection, filter changes, etc.) and monitoring (e.g. conductivity, microbiological analysis) plans;

— record of operator(s) training.

6.3 Performance qualification

The performance qualification should demonstrate the consistency and robustness of the system under local operational conditions. During this phase, information about system behaviour should be collected and action levels should be reviewed or defined. On completion of the performance qualification, the following information should be available:

— test records;

— chemical and microbial analyses;

— key performance indicators [for example, pretreatment efficiency, reverse osmosis (RO) recovery/rejection rate, etc.];

— (initial) trend analysis.

For newly installed systems, the person with overall clinical responsibility for dialysis (possibly supported by technical experts) may authorize use of dialysis fluid for patient treatments once chemical and microbiological analyses are available that show full compliance with the quality requirements of Clause 4, the manufacturer's specifications, and any applicable regulatory requirements.

6.4 Routine monitoring and revalidation

This subclause describes the monitoring activities to be conducted as part of the quality control and quality assurance process.

Routine monitoring should begin following the performance qualification (see 6.3) to ensure ongoing compliance with the dialysis water and dialysis fluid quality requirements set forth in Clause 4. Trend analysis of monitoring data should be used to provide advanced information on system performance, thus enabling a preventive rather than a reactive approach to system maintenance.

Monitoring is achieved with online and offline measurements. Online monitoring of suitable parameters (such as conductivity) provides immediate identification of deviations from normal operating conditions and can identify potential problems in their early stages, and could trigger specific additional offline measurements. A purely time-based offline sampling regime has inherent limitations for the monitoring of a continuous production process since deviations can occur between samples.

Fluid sampling for microbiological testing should be performed no sooner than 24 h after disinfection to avoid false-negative results. When disinfection is performed on consecutive days, or more frequently, samples should be taken before, and as close as practicable to, a disinfection procedure.

Guidance on parameters that should be monitored is provided in Annex C, Table C.1.

A revalidation should be performed under the following circumstances:

— modification of the maintenance and monitoring plans;

— modification of the system;

— changes in the requirements for dialysis fluid quality.

In the absence of system modification, regular revalidation is still required. This revalidation consists of a retrospective assessment of the routine results of the previous year (no additional tests are required

© ISO 2014 – All rights reserved
AVA Documents Document Sharing Hub
Full document details: BS EN ISO 23500:2015

for the revalidation process). The purpose of this review is to prove the adequacy of the maintenance and monitoring plan under the local operating conditions. The revalidation should include a report submitted to, and approved by, the person with overall clinical responsibility for dialysis.

7 Quality management

7.1 General

Quality control and quality assurance procedures should be established to ensure ongoing conformance to policies and procedures regarding fluid quality. This clause defines some of the monitoring activities to be performed at the dialysis facility as part of the quality assurance process. The test methods described in 7.2 do not represent the only acceptable methods available but are intended to provide examples of acceptable methods. The frequency of monitoring is generally recommended by the equipment manufacturer or by local organizations that oversee dialysis facilities. In the absence of a manufacturer's recommendations, guidance on tests to include in a quality assurance monitoring programme can be found in Annex C. This guidance can also be used to supplement the manufacturer's recommendations.

The clinic should establish communications with the feed-water supplier so that the feed-water supplier is aware that the feed water is used for the production of dialysis fluid [i.e. for life-saving treatment on end-stage renal disease (ESRD) patients] and request the establishment of formal procedures to provide the clinic with correct and timely information about any change in the supplied water quality (for example, change of source or type of raw water treatment) or delivery (i.e. water supply interruptions). If such procedures cannot be established, additional monitoring of feed-water quality could be required.

7.2 Monitoring of fluid quality

7.2.1 Monitoring of dialysis water quality

Dialysis water quality should be monitored on a regular basis for the chemical and microbiological contaminants listed in 4.1.2 and 4.1.3. The monitoring schedule should be based on the results of the system validation. For an established water treatment system operating under stable conditions, chemical contaminants in dialysis water should be monitored at least annually. The exception is for total chlorine, which should be monitored as described in 7.3.5.

Methods for monitoring chemical and microbiological contaminants in dialysis water are given in ISO 13959 (see also 8.3).

For water treatment and distribution systems that are integrated into a single system and that have been validated to produce water meeting the quality requirements of ISO 13959, the manufacturer's recommendations for monitoring may be followed for the manufacturer's recommended maximum period of use according to the instructions for use, provided that there is assurance that the system is being operated under the validated conditions.

7.2.2 Monitoring of concentrate quality

Users do not have to test concentrates to demonstrate compliance with the requirements of ISO 13958 when using commercially available packaged chemicals intended for use in preparing liquid concentrates at a dialysis facility or when using commercially available liquid concentrates, provided that the concentrates are manufactured in accordance with the requirements of ISO 13958. If the user prepares concentrate from raw chemicals, the resulting concentrate should meet the requirements of ISO 13958.

© ISO 2014 – All rights reserved

Documents
Document Sharing Hub
Full document details: BS EN ISO 23500:2015

7.2.3 Monitoring of dialysis fluid quality

Dialysis fluid quality should be monitored on a regular basis for the microbiological contaminants listed in 4.3.2 as described in 8.3.1. Methods for monitoring microbiological contaminants in dialysis fluid are described in 8.3.

NOTE 1 Tests for bacterial growth and endotoxins are not required if the system is fitted with an endotoxin-retentive filter validated by the manufacturer and operated and monitored according to the manufacturer's instructions, unless the manufacturer requires those tests in the instructions for use.

NOTE 2 It is not possible to monitor compliance with the bacterial quality requirements for substitution solutions using currently available culturing methods.

Because dialysis fluid is prepared from dialysis water and concentrates meeting the quality requirements of ISO 13959 and ISO 13958, respectively, and since the dialysis water distribution system and dialysis fluid delivery system are required to be constructed of materials that do not contribute chemical contaminants to the water, routine monitoring of chemical contaminants in the dialysis fluid is not required.

7.3 Monitoring of water treatment equipment

7.3.1 General

The following requirements relate to and help explain the guidance provided in Annex C. A brief description of the individual water treatment devices is provided in Annex B.

7.3.2 Monitoring of sediment filters

There is no easy test to determine the effectiveness of a sediment filter; however, pressure drop (ΔP) across the filter can be used to determine when the filter is retaining particulate matter to the point that the filter will no longer allow the required water flow without an excessive reduction in pressure at the outlet of the filter. A backwash cycle is used as a preventive measure to remove particulate matter from the sediment filter and avoid the development of an excessive pressure drop. The frequency of backwashing should follow the manufacturer's recommendations. Sediment filter monitoring should include verification that the timer used to initiate backwashing cycles is set to the correct time of day. A log sheet should be developed to record the pressure drop measurements and timer verifications.

7.3.3 Monitoring of cartridge filters

Cartridge filters should be monitored on a regular basis. There is no easy test to determine the effectiveness of a cartridge filter in removing particulate matter; however, pressure drop (ΔP) across the filter can be used to determine when the filter is retaining particulate matter to the point that the filter will no longer allow the required water flow without an excessive reduction in pressure at the outlet of the filter. A marked decrease in ΔP without a corresponding decrease in flow rate can indicate a loss of filter integrity. Cartridges are usually replaced when ΔP increases to some specified value or at a predetermined interval. A log sheet should be developed to record the pressure drop measurements.

7.3.4 Monitoring of softeners

Softener monitoring consists of the following: testing softened water for residual hardness; for automatically regenerating softeners, checking that the brine tank contains a sufficient supply of undissolved sodium chloride; and, for time-controlled softeners, checking that the timer indicates the correct time of day. The frequency of monitoring should be based on the hardness of the feed water and the capacity of the softener. When reverse osmosis is used, monitoring should be used to ensure that hardness limits established by the reverse osmosis machine manufacturer are not exceeded. A temporary rise in hardness will have a minimal effect on the performance of the reverse osmosis system, as calcium and magnesium are removed by reverse osmosis.

© ISO 2014 – All rights reserved
Documents
Document Sharing Hub
Full document details: BS EN ISO 23500:2015

Testing for hardness should be performed using an ethylenediaminetetraacetic acid (EDTA) titration test, with "dip and read" test strips, or a similar method. Online hardness monitors are also available. If an online monitor is used, it should be used and maintained in accordance with the manufacturer's instructions. Regardless of the method chosen, users should ensure that test accuracy and sensitivity are sufficient to satisfy the hardness monitoring requirements of the reverse osmosis machine manufacturer when the softener is used as pretreatment for a reverse osmosis system.

When timer-controlled softeners are used, it is recommended that the hardness of the water exiting the softener be measured as near as practicable to the end of the duty cycle. The hardness test at the end of the duty cycle will indicate the overall effectiveness of the water softener under worst-case conditions and will ensure that the softener is sized properly and that the regeneration schedule is adequate. Timers should be checked at the beginning of each day. For volume-controlled duplex softeners, testing for hardness can be performed at any time of the day.

The softener brine tank should be monitored on a regular basis to ensure that enough salt is present in the brine tank to form saturated salt solution of sufficient volume for a minimum of one regeneration cycle. Salt used for regeneration should meet the specifications of the softener manufacturer. In particular, salt designated as rock salt should not be used for softener regeneration since it is not refined and typically contains sediments and other impurities that can damage O-rings and pistons and clog orifices in the softener control head. The frequency of monitoring should be based on the length of the duty cycle.

Water softeners should be fitted with a mechanism to prevent water containing the high concentrations of sodium chloride used during regeneration from entering the product-water line during regeneration.

Water hardness test results and verification of timer settings and the presence of salt pellets should be recorded in a water-softener log.

7.3.5 Monitoring of carbon media

The performance of carbon beds is monitored by measuring the total chlorine concentration in the water exiting the carbon bed, or exiting the first carbon bed when a series-connected pair of beds is used. It should be noted that sampling for total chlorine (the sum of free chlorine and chloramine) and allowing a maximum level of 0,1 mg/l of total chlorine is simpler than analysing for free chlorine and chloramine separately.

Testing for total chlorine can be accomplished using the *N*,*N*-diethyl-*p*-phenylenediamine (DPD)-based test kits, dip-and-read test strips based on Michler's thioketone (MTK or TMK), or other methods where comparable sensitivity and specificity can be demonstrated. Online monitors can also be used to measure total chlorine concentrations. If an online monitor is used, it should be used and maintained in accordance with the manufacturer's instructions. Whichever test system is used, it should have sufficient sensitivity and specificity to resolve the maximum levels described in 4.1.2 (see Table 1).

When offline tests are used, testing for total chlorine should be performed at the beginning of each treatment day prior to the patient's initiating treatment. Where chloramine is used to disinfect the potable water supply at a level of 1 mg/l or more, testing should be repeated prior to the beginning of each patient shift; if there are no set patient shifts, testing should be performed approximately every 4 h during operation. More frequent monitoring could be appropriate during temporary operation with a single carbon bed, which can occur following breakthrough of the first bed. In such instances, testing is performed on water exiting the second carbon bed in a series-connected pair. The decision to change the frequency of monitoring should be based on the past performance of the system and on whether changes in feed-water quality have occurred. Samples should be drawn when the system has been operating for at least 15 min. The analysis should be performed onsite since total chlorine levels will decrease if the sample is not assayed promptly.

Results of monitoring should be recorded on a log sheet.

7.3.6 Monitoring of chemical injection systems

Systems for chemical injection should be monitored according to the manufacturer's instructions. If a facility designs its own chemical injection system, procedures should be developed to ensure that

© ISO 2014 – All rights reserved

AVA Documents
Document Sharing Hub
Full document details: BS EN ISO 23500:2015

preparation of the chemical, adequate mixing of the injected chemical with the water flowing through the pretreatment cascade, and reduction to a safe level of the concentration of any chemical residuals before the point of water use. The facility should also verify that the injected chemical does not degrade the performance of downstream devices, such as the reverse osmosis system. Verification can be accomplished by testing samples from the chemical reservoir and the water line after the point of injection for at least three batches of chemical.

When the chemical to be injected is prepared at a facility from powder or by dilution of a liquid concentrate, the chemical injection reservoir should be labelled with the name of the chemical and its concentration, the date the solution was prepared, and the name of the person who mixed the solution. Each batch of chemical should be tested for correct formulation before use. A batch of chemical should not be used or transferred to the injection system reservoir until all tests are completed. The test results, and verification that they meet all applicable criteria, should be recorded and signed by the trained personnel performing the tests.

Protective clothing and an appropriate environment, including ventilation adequate to meet applicable environmental exposure limits, and national standards or regulations should be provided when chemicals for injection are prepared in a dialysis facility.

7.3.7 Monitoring of reverse osmosis

Reverse osmosis systems should be monitored using continuously-reading monitors that measure product-water conductivity [sometimes displayed as total dissolved solids (TDS)]. The measurements can be used to calculate rejection of solutes by the reverse osmosis membrane and provide a measure of equipment performance. Per cent rejection is calculated using the Formula (1):

$$\text{Rejection } (\%) = \frac{\text{Feed water conductivity} - \text{Permeate conductivity}}{\text{Feed water conductivity}} \times 100 \qquad (1)$$

Many reverse osmosis systems have a direct reading for per cent rejection.

The permeate conductivity and rejection are both affected by a number of factors, such as the salinity and composition of the feed water, the water temperature, the level of dissolved gases, and the pressure in the system. Therefore, neither of them should be regarded as a true indicator of the water's suitability for dialysis. No limits are therefore set for these parameters in ISO 13959. Instead, they should be used to monitor changes in performance over time rather than an absolute measure of the quality. This can only be established by performing a chemical analysis of the product water in accordance with ISO 13959.

NOTE 1 For two-stage reverse osmosis systems, the per cent rejection of the second stage will be lower than that of the first stage because of physicochemical phenomena.

Other parameters that should be measured include product and reject stream flow rates and various internal pressures to the extent permitted by the system's instrumentation. Although these parameters are not directly indicative of treated water quality, monitoring them can help ensure that the system is operating within the manufacturer's specifications and, thus, will aid in maintaining the performance of the reverse osmosis membranes. Flow rates can be used to calculate the per cent recovery of the reverse osmosis system using Formula (2):

$$\text{Recovery } (\%) = \frac{\text{Permeate water flow rate}}{\text{Permeate water flow rate} + \text{Reject water flow rate}} \times 100 \qquad (2)$$

NOTE 2 The per cent recovery is also known as the "water conversion factor". The terms are equivalent if none of the reject water stream is recycled to the feed-water stream (see B.2.7). If some of the reject water stream is recycled, Formula (2) provides a measure of overall water utilization by the reverse osmosis system, rather than the recovery of water during a single pass through the membrane module.

NOTE 3 The permeate water flow rate varies with operating pressure and temperature. To enable comparisons to be made under different operating conditions, a normalized permeate flow rate can be calculated. Methods for calculating the normalized permeate flow rate are available from reverse osmosis membrane manufacturers or can be found in ASTM D4516–00 (2010).[164]

© ISO 2014 – All rights reserved
Documents
Document Sharing Hub
Full document details: BS EN ISO 23500:2015

When reverse osmosis is the final process in the water treatment system for removing chemical contaminants, analysis for the contaminants listed in Tables 1 and 2 should be done when the reverse osmosis system is installed to ensure that the limits specified in 4.1.2 are met. It is also recommended that chemical analyses be done when the following situations occur:

— information is obtained from the water supplier that significant changes in the source water, such as seasonal variations, have occurred;

— significant deviations are observed in process parameters, such as pH, conductivity, chlorine concentration and hardness, that can affect the performance of components of the water treatment system;

— reverse osmosis rejection rates decrease by more than 10 %.

All results of measurements of reverse osmosis performance should be recorded daily in an operating log that permits trending and historical review.

7.3.8 Monitoring of deionization

Deionizers shall be monitored continuously using resistivity monitors that compensate for temperatures up to 25 °C and that are equipped with audible and visual alarms. Resistivity monitors shall have a minimum sensitivity of 1 MΩ·cm (1 µS/cm or 0,1 mS/m). If the resistivity of the water at the outlet of a deionizer is less than 1 MΩ·cm, the water shall not be used for dialysis. When deionization is employed as the primary method for removing inorganic contaminants (reverse osmosis is not employed), or when deionization is necessary to polish reverse-osmosis-treated water, chemical analyses to ensure that the requirements of 4.1.2 are met should be performed when the system is installed. Resistivity monitor readings should be recorded on a log sheet twice each treatment day.

7.3.9 Monitoring of endotoxin-retentive filters

The performance of endotoxin-retentive filters in dialysis water distribution, bicarbonate concentrate distribution, or dialysis fluid delivery systems can be monitored by testing the fluid that is directly exiting the filter for bacteria and endotoxins. Endotoxin-retentive filters should be fitted with a means of assessing filter integrity and fouling. One suitable means is to monitor the pressure drop (ΔP) across the filter at a given product fluid flow rate using pressure gauges on the inlet (feed) and outlet (product) streams. Alternatively, product fluid flow rate can be measured at a given pressure drop. Such monitoring can indicate when membrane fouling has progressed to the point that membrane replacement or cleaning is needed. Monitoring is also necessary to ensure that the device is being operated in accordance with the manufacturer's instructions. Endotoxin-retentive filters operated in the cross-flow mode should also be monitored in terms of the flow rate of fluid being directed to drain at a given pressure drop. Results of pressure measurements and bacteria and endotoxin levels should be recorded on a log sheet.

7.4 Monitoring of dialysis water storage and distribution

NOTE 7.4.1 to 7.4.3 relate to and help explain Table C.1.

7.4.1 Monitoring of water storage tanks

For a system that distributes dialysis water to single-patient proportioning systems, routine monitoring of water storage tank for total viable microbial count and endotoxin concentration is generally accomplished indirectly by monitoring the dialysis water at the first outlet to the distribution loop. For routine monitoring of a storage tank that supplies dialysis water to a central dialysis fluid delivery system, or when direct monitoring of a dialysis water storage tank is performed as part of a troubleshooting process, the total viable microbial count and endotoxin concentration should be determined using samples drawn from a port at the outlet of the storage tank. When a change has been made to an existing storage tank, more frequent testing should be considered to verify that bacteria or endotoxin levels are consistently within the allowed limits. The need for additional testing should be based on the original validation plan (see 6.1) and a risk analysis of the likely impact of the change on system performance.

© ISO 2014 – All rights reserved

Documents
Document Sharing Hub
Full document details: BS EN ISO 23500:2015