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

Part 1: General requirements

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

Partie 1: Exigences générales

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Foreword

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The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO document should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

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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*, in collaboration with the European Committee for Standardization (CEN) Technical Committee CEN/TC 205, *Non-active medical devices,* in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

This second edition cancels and replaces the first edition (ISO 23500-1:2019), which has been technically revised.

The main changes are as follows:

— WHO Drinking Water Guideline has been used as the main drinking water quality reference instead of the US EPA or other European standards;

— thallium has been removed from the list of contaminants, as no studies have reported data to indicate that this contaminant is of particular concern in the haemodialysis setting;

— alternative water treatment technologies (e.g. reverse osmosis pre-treatment with ultrafiltration) have been included in the subclauses dealing with water treatment technology (refer to B.2.7 and B.2.8);

— a new annex (Annex H) has been added to provide clarification of the different water quality monitoring approaches (online versus offline monitoring);

— the microbiological analytic methods have been updated to include endotoxin testing using recombinant Factor C (rFC), flow cytometry, autofluorescence and rapid tests (e.g. ATP);

— a new annex (Annex I) has been added to provide guidance on risk assessment;

— the validation of water treatment systems has been revised to include validation steps (e.g. installation qualification, operational qualification, performance qualification and revalidation);

— further guidance has been added on technical needs after the typical technical interventions in Clause E.4.

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

This document is the base standard for standards dealing with water treatment and the production of dialysis fluid in the ISO 23500 series.

The objective of the ISO 23500 series is to provide users with guidance for handling water and concentrates and for the production and quality oversight 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.

Annex A provides further information on the rationale for the development and provisions of this document.

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 document provides guidance on quality oversight and maintenance of the equipment to ensure that dialysis fluid quality is acceptable at all times. At various places in this document, the user is advised to follow the manufacturer's instructions regarding the operation and maintenance of equipment. In 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 further information on 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 can be required and how it should be configured; the descriptions are not intended to be detailed design standards. Requirements for water treatment equipment are provided in ISO 23500-2.

Increasingly, self-contained, integrated systems designed and validated to produce water and dialysis fluid are becoming available and used clinically. This document applies to systems assembled from individual components. Consequently, some of the requirements in ISO 23500-1 and ISO 23500-2 do not apply to integrated systems, however such systems are required to comply with the requirements of ISO 23500-3, ISO 23500-4 and ISO 23500-5. In order to ensure conformity when using such systems, adherence to the manufacturer's instructions regarding the operation, testing and maintenance of such systems is required to ensure that the system is being operated under the validated conditions.

This document 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 surveillance of dialysis fluid for haemodialysis and protecting haemodialysis patients from adverse effects arising from known chemical and microbial contaminants that can be found in improperly prepared dialysis fluid.

Annexes F and G provide further information regarding the special considerations for home and acute haemodialysis. This document together with its constituent parts is directed towards the healthcare professionals involved in the management or routine care of haemodialysis patients and responsible for the quality of 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.

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

Part 1:
General requirements

1 Scope

This document specifies the general requirements for the preparation of fluids for haemodialysis and related therapies and substitution fluid for use in online therapies, such as haemodiafiltration and haemofiltration, for dialysis practitioners. This document gives guidance on the user's responsibility for fluids used in haemodialysis and related therapies once the equipment used in its preparation has been delivered and installed. As dialysis water used to prepare dialysis fluid can also be used to reprocess dialysers not marked intended for single use, this aspect of water use is also covered by this document.

This document is applicable to

— 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.

— the quality management of the equipment used to prepare acid and bicarbonate concentrate from powdered or other highly concentrated media at a dialysis facility, and

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

This document 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 pre-packaged solutions, and

— systems and solutions for peritoneal dialysis.

This document does not address clinical issues associated with inappropriate usage of such fluids.

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 23500-2, *Preparation and quality management of fluids for haemodialysis and related therapies — Part 2: Water treatment equipment for haemodialysis applications and related therapies*

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

ISO 23500-5, *Preparation and quality management of fluids for haemodialysis and related therapies — Part 5: Quality of dialysis fluid for haemodialysis and related therapies*

3 Terms and definitions

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

ISO and IEC maintain terminology databases for use in standardization at the following addresses:

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

— IEC Electropedia: available at https://www.electropedia.org/

3.1
acetate concentrate
concentrated solution of salts containing acetate, which when diluted with *dialysis water* (3.17), yields bicarbonate-free *dialysis fluid* (3.15) for use in dialysis

Note 1 to entry: Acetate concentrate can 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
low pH mixture of salts that, when diluted with *dialysis water* (3.17) and *bicarbonate concentrate* (3.6), yields *dialysis fluid* (3.15) for use in dialysis

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

Note 2 to entry: Acid concentrate can contain glucose.

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

3.3
action level
value from monitoring that necessitates immediate intervention

[SOURCE: ISO 13408-1:2023, 3.1, modified — the word particulate has been excluded.]

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

3.5
bacteria and endotoxin-retentive filter
BERF
endotoxin retentive filter
ERTF
membrane filter used to remove *endotoxins* (3.20) and microorganisms from *dialysis water* (3.17) or *dialysis fluid* (3.15)

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

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

3.6
bicarbonate concentrate
B-concentrate
concentrated preparation of sodium bicarbonate that, when diluted with *dialysis water* (3.17) and *acid concentrate* (3.2), makes *dialysis fluid* (3.15) used for dialysis

Note 1 to entry: Some bicarbonate concentrates also contain sodium chloride.

Note 2 to entry: Bicarbonate concentrate can be in the form of a liquid or a dry powder.

Note 3 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.

3.7
biofilm
microbially-derived sessile community characterized by cells that are irreversibly attached to a substratum or interface or to each other, are embedded 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* (3.17) systems. When the level of biofilm is such that the *action levels* (3.3) for microorganisms and *endotoxins* (3.20) in the dialysis water are routinely reached or exceeded, 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.

3.8
bulk delivery
delivery of large containers of concentrate to a dialysis facility

Note 1 to entry: Bulk delivery canbe containers such as drums, which can be pumped into a *storage tank* (3.41) maintained at the *user*'s (3.44) 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.

3.9
central concentrate system
system that prepares and/or stores concentrate at a central point for subsequent distribution to its points of use

3.10
central dialysis fluid delivery system
system that produces *dialysis fluid* (3.15) from *dialysis water* (3.17), and concentrate or powder at a central point, and that distributes the dialysis fluid from the central point to individual dialysis machines

3.11
combined chlorine
chlorine that is chemically combined with other compound(s), such as ammonia, and that results in the production of chloramine

Note 1 to entry: There is no direct test for measuring combined chlorine, but it can be established indirectly by measuring both total and *free chlorine* (3.12) and calculating the difference.

3.12
free chlorine
chlorine present in water as dissolved molecular chlorine (Cl_2), hypochlorous acid (HOCl) and hypochlorite ion (OCl^-)

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

3.13
total chlorine
sum of *free chlorine* (3.12) and *combined chlorine* (3.11)

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.

3.14
colony-forming unit
CFU
aggregation of microorganisms arising from a single cell or multiple cells

[SOURCE: ISO 11139:2018, 3.53, modified — "visible" has been deleted at the beginning of the definition.]

3.15
dialysis fluid
DEPRECATED: dialysate
DEPRECATED: dialysis solution
aqueous fluid made from *dialysis water* (3.17) containing electrolytes and, usually, buffer and glucose, that is delivered to the dialyser by the *dialysis fluid delivery system* (3.16), which is intended to exchange solutes with blood during *haemodialysis* (3.24) and *haemodiafiltration* (3.23)

Note 1 to entry: ISO 23500-5 defines three levels of dialysis fluid in terms of microbiology: standard dialysis fluid, ultrapure dialysis fluid and online-prepared *substitution fluid* (3.42) used for haemodiafiltration.

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 pre-packaged parenteral fluids used in some renal replacement therapies, such as haemodiafiltration and *haemofiltration* (3.25).

3.16
dialysis fluid delivery system
device that

— prepares *dialysis fluid* (3.15) online from *dialysis water* (3.17) and concentrates, or 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* (3.18) 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 dialysis fluid delivery systems.

Note 2 to entry: The dialysis fluid delivery system can be an integral part of the dialysis machine or a centralized preparation system which feeds multiple individual dialysis consoles.

Note 3 to entry: Dialysis fluid delivery systems are also known as *proportioning systems* (3.34) and dialysis fluid supply systems.

3.17
dialysis water
water that has been treated to meet the requirements of ISO 23500-3 and which is suitable for use in *haemodialysis* (3.24) applications, including the preparation of *dialysis fluid* (3.15), reprocessing of dialysers, preparation of concentrates and preparation of *substitution fluid* (3.42) for online convective therapies

Note 1 to entry: Some integrated, validated systems, and other new systems by alternative design can provide ultrapure dialysis water with <0,1 CFU/ml and <0,03 EU/ml. By mixing with *sterile* (3.40) and *non-pyrogenic* (3.31) concentrates and by utilising sterile and non-pyrogenic dialysis fluid pathway, ultrapure dialysis fluid can be produced in such integrated and validated systems.

3.18
disinfection
process to reduce the number of viable microorganisms to a level specified as appropriate for a defined purpose

3.19
empty-bed contact time
EBCT
measure of the time during which water to be treated is in contact with the treatment medium in a contact vessel, assuming that all liquid passes through the vessel at the same velocity

Note 1 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.

Note 2 to entry: EBCT, expressed in minutes, is calculated from:

$$t_{EBCT} = v/q$$

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).

3.20
endotoxin
lipopolysaccharide component of the cell wall of Gram-negative bacteria that is heat stable and that elicits a variety of inflammatory responses in humans

Note 1 to entry: See also *pyrogen* (3.35).

[SOURCE: ISO 11139:2018, 3.101, modified — "animals and" has been deleted from the definition and Note 1 to entry has been added.]

3.21
endotoxin unit
EU
unit assayed by the *Limulus* amoebocyte lysate (LAL) test when testing for *endotoxins* (3.20)

Note 1 to entry: As the activity of endotoxins depends on the bacteria from which they are derived, their activity is evaluated by reference 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.

3.22
germicide
agent that kills microorganisms

3.23
haemodiafiltration
process whereby concentrations of water-soluble substances in a patient's blood and an excess of fluid of a patient are corrected by a simultaneous combination of *haemodialysis* (3.24) and *haemofiltration* (3.25)

[SOURCE: IEC 60601-2-16:2018, 201.3.208]

3.24
haemodialysis
process whereby concentrations of water-soluble substances in a patient's blood and an excess of fluid of a patient are corrected by bidirectional diffusive transport and ultrafiltration across a semi-permeable membrane separating the blood from the *dialysis fluid* (3.15)

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

[SOURCE: IEC 60601-2-16:2018, 201.3.209, modified — Note 1 to entry has been added.]

3.25
haemofiltration
process whereby concentrations of water-soluble substances in a patient's blood and an excess of fluid of a patient are corrected by convective transport via ultrafiltration and partial replacement by a *substitution fluid* (3.42) resulting in the required net fluid removal

Note 1 to entry: Convective transport is achieved by ultrafiltration across a high flux membrane. Fluid balance is maintained by the infusion of a replacement solution into the blood either before the haemofilter [predilution *haemofiltration* (3.25)] or after the haemofilter (post-dilution haemofiltration) or a combination of the two (mixed dilution haemofiltration).

Note 2 to entry: There is no *dialysis fluid* (3.15) stream in haemofiltration.

[SOURCE: IEC 60601-2-16:2018, 201.3.211, modified — Notes 1 and 2 to entry have been added.]

3.26
heterotrophic
organism that cannot produce its own food, instead taking nutrition from other sources of organic compounds for metabolic synthesis

3.27
initial validation
complete *validation* (3.45) of the entire *water treatment system* (3.48) or *dialysis fluid* (3.15) preparation systems following installation

Note 1 to entry: Initial validation is performed on new systems, completely unknown systems or a system following major repairs, where new and previous version of system are not comparable (values of validations are not comparable). In systems without major changes, initial validation is performed only once in the lifetime of a system. Initial validation is subdivided into prospective initial validation and concurrent initial validation.

3.28
***Limulus* amoebocyte lysate test**
LAL test
test for measuring bacterial *endotoxins* (3.20) using *Limulus* amoebocyte lysate reagent

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: Amoebocyte lysate from a second horseshoe crab, *Tachypleus tridentatus*, may also be used to detect endotoxins.

[SOURCE: ISO 29701:2010, 2.7, modified — Note 1 to entry has been replaced and Note 2 to entry has been added.]

3.29
manufacturer
entity that designs, makes, fabricates, assembles or processes a particular item or object

Note 1 to entry: Manufacturer includes, but is 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.

Note 2 to entry: Manufacturer does not cover the preparation of concentrates from pre-packaged dry chemicals at a dialysis facility or the handling of bulk concentrates at a dialysis facility as responsibility for the concentrate is transferred from the manufacturer to the *user* (3.44).

3.30
microbial contamination
presence of unintended bacteria, fungi, protozoa or viruses

[SOURCE: ISO 11139:2018, 3.171]

3.31
non-pyrogenic
not pyrogenic
not eliciting a *pyrogen* (3.35) reaction

Note 1 to entry: This definition is applicable for fluids produced by online techniques, e.g. substitution and priming fluids.

Note 2 to entry: For medical devices and injectable fluids, the threshold pyrogenic dose (the minimum dose that produces fever) is set at 5 EU/kg/h. The commonly used gel clot method has a sensitivity limit of 0,03 EU/ml, enabling the volume of fluid that may be administered without breaching the threshold pyrogenic dose to be established.

3.32
operational qualification
OQ
verification (3.46) of the correct operation of the system and comparison of the system performance with the systems functional performance

3.33
product water
water produced by a *water treatment system* (3.48) or an individual device thereof

3.34
proportioning system
apparatus that proportions *dialysis water* (3.17) and *haemodialysis* (3.24) concentrate to prepare *dialysis fluid* (3.15)

3.35
pyrogen
fever-producing substance

Note 1 to entry: Pyrogens are most often lipopolysaccharides of gram-negative bacterial origin [see also *endotoxin* (3.20)].

3.36
retrospective validation
annual *validation* (3.45) for a system

Note 1 to entry: The initial or first retrospective validation is performed 12 months after ending of initial validation period and repeated thereafter annually. The purpose of the validations is to prove the adequacy of the system design, as well as of the maintenance and monitoring protocols as defined during the *operational qualification* (3.32) and performance qualification phases under the local operating conditions. A *revalidation* (3.37) (new validation) is required in the event of

— modification of the maintenance and surveillance plans (includes performance qualification as applicable);

— modification to the system (includes *initial validation* (3.27), operational qualification and performance qualification);

— changes in the requirements for *dialysis fluid* (3.15) quality;

— changes in the feed water quality outside the acceptable limits previously foreseen.

Note 2 to entry: Annual retrospective validation may be replaced by measures that continuously verify that necessary requirements are met. (continuous validation) If, by introducing additional procedures and policies (and by using software solutions) to perform all the activities undertaken during retrospective validation, continuously instead of once in every 12 months, then annual retrospective validation may be replaced by measures that continuously verify that necessary requirements are met, i.e. by continuous validation.

Note 3 to entry: In the absence of system modification, retrospective validation is still required. Under such circumstances, the retrospective validation consists of the retrospective assessment of the routine results over the previous 12 months with no additional tests together with a written report submitted to, and approved by, the person with overall clinical responsibility for dialysis.

3.37
revalidation
repeat of the different qualification steps of a system or part of system which already have been validated

Note 1 to entry: Revalidation is required following changes of *disinfection* (3.18) frequency (less frequent), changes of sampling frequency, specific minor repairs, specific changes of some requirements, etc. Most commonly revalidation involves disinfection frequency revalidation (first phase performance qualification, PQ-1) and/or sampling frequency revalidation (second phase performance qualification, PQ-2).

3.38
sodium hypochlorite
chemical used for *disinfection* (3.18) of *haemodialysis* (3.23) systems

Note 1 to entry: Commercially available solutions of sodium hypochlorite are known in different countries by terms such as bleach and L'eau de Javel. These solutions are used for disinfection at concentrations recommended by equipment *manufacturers* (3.29).

3.39
source water
water entering a dialysis facility from an external supply, such as a municipal *water supply* (3.47)

Note 1 to entry: Source water, is sometimes referred to as feed or raw water, and is generally water suitable for drinking (potable water) and meeting the requirements for drinking water.

3.40
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. an 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 appropriate sections of the applicable pharmacopoeia to produce a solution free from microorganisms for the validated life of the filter.

3.41
storage tank
tank at the *user*'s (3.44) facility for storage of *dialysis water* (3.17) or concentrate from bulk deliveries, or for concentrate prepared in bulk at the user's facility from powder and dialysis water

3.42
substitution fluid
substitution solution
replacement solution
fluid used in *haemofiltration* (3.25) and *haemodiafiltration* (3.23) treatments which is infused directly into the patient's blood as a replacement for the fluid that is removed from the blood by ultrafiltration

Note 1 to entry: Substitution fluid can also be used for administering a bolus, priming an extracorporeal blood circuit and returning blood to the patient at the end of a treatment.

3.43
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 evaluate the performance of reverse osmosis units. TDS values are expressed in milligrams per litre (mg/l), in terms of

— $CaCO_3$,

— NaCl,

— KCl, or

— TDS 442 equivalents [TDS 442 is a solution of sodium sulfate (40 %), sodium bicarbonate (40 %), and sodium chloride (20 %) that closely represents the conductivity to concentration relationship, for natural freshwater].

3.44
user
responsible physician, their representative or healthcare professional with a responsibility for the prescription, production and delivery of *dialysis fluid* (3.15)

Note 1 to entry: In this context, the user refers to the decision maker who is accountable for the clinical care of the patients.

3.45
validation
process of documenting that the *dialysis water* (3.17) treatment and *dialysis fluid* (3.15) production systems, when installed and operated according to the *manufacturer*'s (3.29) recommendations, consistently produces 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: Different types of validation exist e.g. *initial validation* (3.27), *retrospective (annual) validation* (3.36) and *revalidation* (3.37).

3.46
verification
process of demonstrating that the system complies with applicable regulations, specifications or other conditions

3.47
water supply
input supplied to a *water treatment system* (3.48) or to an individual component of a water treatment system

Note 1 to entry: The water supplied to the water treatment system, sometimes referred to as feed water, is water that meets drinking water requirements.

3.48
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 23500-3 for *haemodialysis* (3.24) applications and deliver it to the point of use

4 Quality requirements

4.1 General

The quality requirements set forth in this document with respect to dialysis water (see 4.2), concentrates (see 4.3), and dialysis fluid (see 4.4) are identical to those in ISO 23500-4, ISO 23500-3 and ISO 23500-5. The

latest editions of these documents should be consulted to ascertain if there have been any changes to quality requirements before implementing the recommendations of this document.

4.2 Dialysis water

4.2.1 General

The requirements contained in 4.2 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 4.2.

NOTE Some integrated validated systems, such as two stage RO systems with bacterial and endotoxin retentive filters, and other new systems by alternative design are capable of producing highly purified dialysis water with <0,1 CFU/ml and <0,03 EU/ml at a stage in their system prior to mixing with concentrates to produce ultrapure dialysis fluid.

4.2.2 Chemical contaminants in dialysis water

Chemical contaminants present in potable water can pose a risk to the patient receiving dialysis treatment. Contaminants identified as needing restrictions on their allowable level in dialysis water compared with potable water have been divided into three groups: chemicals known to cause toxicity in dialysis patients; physiological substances that can adversely affect the patient if present in the dialysis fluid in excessive amounts and trace elements. The maximum allowable levels of these contaminants are listed in Tables 1 and 2 and include the anticipated uncertainty associated with the analytical methodologies listed in ISO 23500-3:2024, Table 4.

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.

Conformity shall be shown by:

— using analytical methods referenced in ISO 23500-3 or other appropriately validated and comparable analytical methods, or

— when analytical methodology for the individual trace elements listed in Table 2 is not available and the water can be demonstrated to meet the standards for potable water as defined by the WHO,[18] an analysis for total heavy metals with a maximum allowable level of 0,1 mg/l may be used, or

— if neither of the above options are available, conformity with the requirements of Table 2 can be met by using water that can be demonstrated to meet the potable water requirements of the WHO and a reverse osmosis system with a rejection of >90 % based on conductivity, resistivity or TDS.

Samples for chemical examination shall be collected from sampling points situated at the end of the water treatment cascade or at the most distal point of at least one of water distribution loops.

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 23500-3 at the time of installation.

Following the installation of a water treatment, storage and distribution system, the user is responsible for regularly surveying the levels of chemical contaminants in the dialysis water and for complying with the requirements of this document.

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

Class of contaminants	Contaminant	Maximum concentration mg/l[c]
Contaminants with documented toxicity in haemodialysis	Aluminium	0,01
	Total chlorine[d]	0,1
	Copper	0,1
	Fluoride	0,2
	Lead	0,005
	Nitrate (as N)	2
	Sulfate	100
	Zinc	0,1
Electrolytes normally included in dialysis fluid	Calcium	2 (0,05 mmol/l)
	Magnesium	4 (0,15 mmol/l)
	Potassium	8 (0,2 mmol/l)
	Sodium	70 (3,0 mmol/l)

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

[b] The reader is cautioned to refer to ISO 23500-3 to ensure that there have been no changes to this table.

[c] Unless otherwise noted.

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

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

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

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

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

[a] The reader is cautioned to refer to the latest edition of ISO 23500-3 to ensure that no changes have been made to the maximum concentrations shown.

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

4.2.3 Organic carbon, pesticides and other chemicals

Table 2 excludes organic compounds such as pesticides, perfluorinated chemicals, polycrylic aromatic hydrocarbons and pharmaceutical products. It is recognised that such compounds can be present in the water supply, and their presence is receiving considerable attention from environmentalists and regulatory authorities. Prolonged exposure can result in bio accumulation and adverse health outcomes, however in the context of haemodialysis patients, the consequences of exposure are poorly understood and have received limited study[19],[20].

If such compounds are of concern, the suggested starting point is to establish levels and compare these to national regulations and standards for drinking-water quality.

Organic compounds can be effectively removed by the use of activated carbon beds or filters, the dialysis facility should consider dimensioning of beds and filters to ensure that there is sufficient capacity to remove organic compounds, should the need arise. If carbon valences are largely occupied by chlorine/chloramine, they will not be available to bind organic contaminants. Nanofiltration and reverse osmosis are also capable of significant rejection of many such compounds.

4.2.4 Microbiological contaminants in dialysis water

The total viable microbial count (TMVC) and endotoxin concentration in dialysis water shall comply with the maximum allowable levels specified Table 3. Action levels for the total viable microbial count and endotoxin concentration shall also be set, based on the 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 23500-3 at the time of installation.

Following the installation of a water treatment, storage and distribution system, the user is responsible for regularly surveying the microbiology of the system and for complying with the requirements of this document, including those requirements related to action levels. Clause 8 details strategies for microbiological control. Annex C provides further information related to surveillance.

In association with the presence of bacteria and endotoxin in the water, yeast and filamentous fungi can also be present. No specific recommendations have been made with respect to the routine measurement of such contaminants, nor have action limits been set.

Table 3 — Maximum allowable levels for TMVC and endotoxins in dialysis water[a]

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

[a] The reader is cautioned to refer to ISO 23500-3 to ensure that there have been no changes to the values presented in this table.

[b] The typical action level is generally set at 50 % of the maximum allowable level. Other values can be set.

4.3 Requirements for concentrate

4.3.1 Chemical and microbiological contaminants in concentrate

Concentrates used to prepare the dialysis fluid shall comply with the quality requirements specified in ISO 23500-4.

Bicarbonate concentrate can grow bacteria and caution should be used to limit the bacterial levels in bicarbonate concentrate. Dialysis fluid can also be prepared from acetate concentrate used as a single concentrate that can be metabolized by the patient to bicarbonate.

4.3.2 Water used to prepare concentrate

Water used to prepare concentrates at a dialysis facility shall meet the requirements of ISO 23500-3. Any concentrate prepared at a dialysis facility shall permit the dialysis machine to prepare dialysis fluid meeting the requirements of ISO 23500-5.

4.4 Requirements for dialysis fluid

4.4.1 General

The requirements contained in 4.4 apply to a sample of the dialysis fluid collected as close as practicable to the inlet to the dialyser.

ISO 23500-5 defines three levels of dialysis fluid: standard dialysis fluid, ultrapure dialysis fluid and online-prepared substitution fluid used for haemodiafiltration.

Standard dialysis fluid shall be regarded as the minimum acceptable quality. Ultrapure dialysis fluid is a step forward in improving biocompatibility, reducing inflammation and preventing dialysis related complications.

Tests for bacterial growth and endotoxins are not required for ultrapure dialysis, or "online" prepared substitution fluids, if the dialysis machine fluid pathway is fitted with a filter of an appropriate capacity to retain bacteria and endotoxins that is validated by the manufacturer, and operated and monitored according to the manufacturer's instructions, unless the manufacturer requires such tests in the instructions for use.

4.4.2 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 23500-5 and reproduced in Table 4. Action levels for the total viable microbial count and endotoxin concentration shall also be set, based on the knowledge of the microbial dynamics of the system as specified in ISO 23500-5. Typically, the action level is set at 50 % of the maximum allowable level for total viable microbial count and endotoxins. If the 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.

Tests for bacterial growth and endotoxins are not required for ultrapure dialysis or "online" prepared substitution fluids if the dialysis machine fluid pathway is fitted with a filter of an appropriate capacity to retain bacteria and endotoxins that is validated by the manufacturer, and operated and monitored according to the manufacturer's instructions, unless the manufacturer requires such tests in the instructions for use.

Table 4 — Maximum allowable levels for TMVC and endotoxins in dialysis fluids[a]

Contaminant	Standard dialysis fluid		Ultrapure dialysis fluid
	Maximum allowable level	Action level[b]	Maximum allowable level
TMVC	<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 edition of ISO 23500-5 to ensure that there have been no changes to this table.

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

4.4.3 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 23500-5 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 surveillance of the dialysis fluid bacteriology of the total system following installation.

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

4.4.4 Microbiological requirements for online-prepared substitution fluid

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

This fluid shall be sterile and non-pyrogenic in accordance with ISO 23500-5.

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

The user shall follow the manufacturer's instructions for the installation, use, maintenance and conformity of the validated system. The function of the validated system shall be verified in accordance with the manufacturer's instructions at the time of installation and confirmed by the user with regular surveillance. Surveillance 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 23500-4 and ISO 23500-3.

4.5 Record retention

In the absence of national regulations, retain records of installation, surveillance, maintenance and disinfection of the water treatment and dialysis fluid preparation systems, medical observation, and personnel training and education, for the same period as clinical records.

5 System design and technical considerations

5.1 General

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 23500-2, with special regard to the aspects related to the dialysis water quality, disinfection and maintenance. Reference to specialist guidance on the design and operation of building and engineering technology applicable to healthcare delivery should be made.

The treatment of water for haemodialysis applications is an energy and resource intensive process and, in designing the system, appropriate consideration should also be given to ensure optimal use of resources, e.g. water and energy.

In regions where natural hazards such as earthquakes or weather events are expected, it is recommended to consider the measures that can enable dialysis treatments to be undertaken after such events, e.g. consideration of an emergency power and water supply[21],[22].

Concentrates used with the treated water to prepare dialysis fluid are obtained from a supplier in a ready-to-use form or prepared at the dialysis facility from dialysis water and pre-packaged salts. The technical features of the concentrate preparation and distribution component of the system should be based on the criteria listed in ISO 23500-4.

The spent or used dialysis fluid is discharged into the public sewage system without treatment. Disinfectant solutions can also be similarly discharged. The risks to public health and the environment from such discharges are negligible, however, such discharges can impact the effectiveness of domestic anaerobic digestion systems.

5.2 Technical aspects

According to the requirements listed in ISO 23500-2, the system design should specifically address the following points.

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

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

   2) the microbiological load which can require the introduction of an additional chlorination step;

   3) the flow rates, pressure and temperature;

   4) the treatment techniques used by the provider of the feed water (e.g. addition of chloramine, fluoride, aluminium sulfate or other chemicals); because treatment techniques can change, ongoing communication with the provider of the feed water is recommended.

   If the water supply to the treatment system is not directly from the municipal distribution network, but comes via an existing hospital water supply, there should be awareness of the potential risks that can arise from the introduction of chemicals into the hospital's water supply by hospital engineering staff. To prevent the occurrence of adverse effects arising from such actions, the introduction or addition of chemicals into the hospital water supply should only be undertaken after prior consultation with renal services. It should be further noted that, if such chemicals are introduced, it can necessitate additional surveillance prior to water being used for dialysis applications.

b) If heat disinfection is planned for the system, the distribution loop is sanitized along with the links from the distribution loop to the dialysis machines. The demand for water during such disinfection is higher than required by the dialysis machines during operation.

c) Commonly, reverse osmosis systems capacity is rated at a specified incoming water temperature. There should be awareness that, during the winter months, a failure to attain the specified temperature will lead to a reduced system efficiency. In order to meet the required water demand, pre-heating of the feed water or the installation of a system with increased capacity to compensate for the reduction in reverse osmosis efficiency during the winter months can be required.

d) Disinfection of the system is the only effective method of diminishing and inactivating microflora. First and foremost, the frequency of disinfection is important. Disinfection should be performed on a regular basis to limit biofouling within the fluid pathways of the system. Second, all surfaces in the circuit should be included in the disinfection procedure. This includes the reverse osmosis membranes (especially the clean side), the distribution piping, the inlet lines to the dialysis machines (located before the disinfection circuit of the dialysis machine) and the dialysis machines (which have their own disinfection circuit and programme). Third, the disinfection procedure, when applied with a given frequency and with inclusion of all critical areas, should be capable of minimizing the effects of bio-fouling.

   Disinfection can be performed using heat or chemicals. Ultraviolet (UV) lamps can be used to inactivate planktonic cells but are of no value against any biofilm that has formed in the system.

   Hot water can be used to control bacterial proliferation in dialysis water storage and distribution systems. The exposure time should be according to the manufacturer’s instructions. The water heater of a hot water disinfection system should be capable of delivering hot water at the temperature and for the exposure time specified by the manufacturer to any site in the dialysis water storage and distribution system. The manufacturer’s instructions for using hot water disinfection systems should be followed.

   If chemical disinfection has to be used, the period prior to the next dialysis treatment should be sufficient to enable the chemicals to be rinsed completely from the system.

   If it is possible to sanitize the haemodialysis machines at the same time as the distribution loop, then sanitization of both should be performed since this is the easiest and simplest method.

e) Provision for adequate process surveillance should be made.

f) 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 pre-treatment section of the water treatment system be designed to supply the main purification device (usually reverse osmosis) with the feed water meeting the specifications for that device, i.e. pressure, temperature, flow and quality (e.g. elimination of chemicals which cannot be effectively removed by the main purification device or that can damage it).

NOTE Local water and building regulations for system design can apply.

5.3 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 including central concentrate systems. For this reason, the system should be designed to reduce, as much as possible, potential sources of contamination and to allow effective surveillance 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 should 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.

At a minimum, sampling ports at the end of the distribution loops shall be available. For troubleshooting purposes, an additional sampling port at the start of the distribution loops should also be available.

5.4 Environmental impact

The environmental impact of haemodialysis is considerable in terms of the resources used. e.g. water and electricity. In planning the water treatment, consideration should be given to minimizing the water that is rejected by the reverse osmosis (RO) system, for example, by the use of a double pass system, in which any water that would be disposed of as wastewater is recirculated through the semi-permeable membrane. This can be achieved by using either two entirely different RO systems or by configuring a single RO system in a two-pass configuration and/or the use of rejected water for applications that do not require drinking water, e.g. flushing toilets.

Treatment of patients may take place in a hospital, clinic or a home environment. When the patient is receiving treatment in their home, the patient should be aware that the discharge of large volumes of fluid associated with dialysis treatment in the form of used dialysis fluid or disinfection products associated with the water treatment maintenance can impact the effectiveness of a domestic anaerobic digestion system. Local regulations can be in place to limit such discharges into public sewage systems.

6 Validation of system performance

6.1 General

The validation process should document evidence that the system consistently produces dialysis water and dialysis fluids meeting the quality requirements of ISO 23500-3 or ISO 23500-5.

The validation process consists of the following:

— assignment of operational responsibility;

— assignment of clinical responsibility;

— assignment of legal responsibility;

— validation plan;

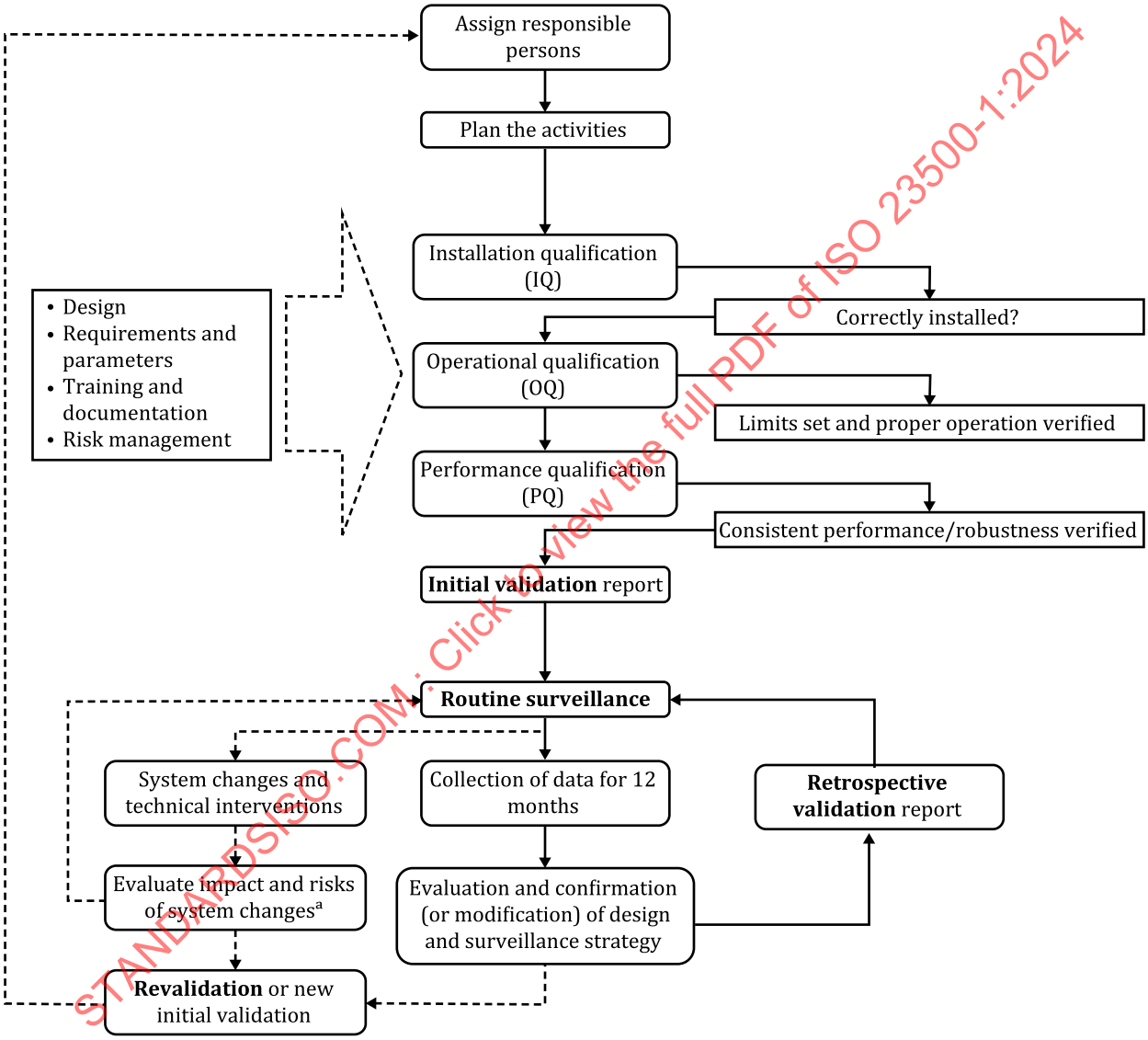
— installation and operational qualification;

— performance qualification;

— revalidation as it relates to routine surveillance.

Annex E provides further information on the validation process.

An example of the validation process for a fluid preparation and distribution system is presented in Figure 1.



Key

→ indispensable validation process steps

⇢ other validation process steps

[a] Table E.2 can be used as a guide.

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

6.2 Validation plan

The validation plan should be presented in a clear and concise document covering

— a description of the relevant systems, equipment or processes;

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

— the 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 the overall responsibility for dialysis fluids.

6.3 Installation and operational qualification

The installation qualification (IQ) defines and provides the documented proof that the system is installed according to 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 the operator's manuals. The installation should be carried out by qualified personnel according to the manufacturer's documented recommendations.

The installation qualification should be followed by an operational qualification (OQ) which compares the system performance with the system functional specification. Operational qualification verifies the correct operation of the system, including its range of operation, set point, interlock and functional testing. On completion of this phase, the following information should be available:

— test records;

— set-up record;

— calibration schedule;

— sampling procedures;

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

— record of operator(s) training.

6.4 Performance qualification

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

— test records;

— chemical and microbial analyses;

— key performance indicators (e.g. pre-treatment efficiency, RO recovery/rejection rate);

— the (initial) trend analysis.

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

In some instances, the schematic approach shown in Figure 1 cannot be followed and concurrent validation can be appropriate, for example, following major refurbishment of an already existing system. The person with overall clinical responsibility for dialysis (supported by technical experts) may authorize the use of dialysis fluid for patient treatments, provided an appropriate risk assessment has been performed and recorded (see Annex I for guidance).

Risk influencing factors can be related to:

— type, application and frequency of disinfection;

— integration of supply lines to dialysis machines;

— material and age of the dialysis water system;

— microbiological quality of the previous installation;

— risk of suspending a dialysis session or prescription changes (e.g. dialysis technique);

— filter technology [e.g. dialysis machines fitted with bacteria and endotoxin retentive filters (BERFs)].

6.5 Validation

6.5.1 General

The purpose of validation is to prove the adequacy of the system design, as well as the effectiveness of maintenance and monitoring protocols as defined during the OQ and PQ under local operating conditions.

6.5.2 Initial validation

Initial validation (IQ, OQ and PQ) of the entire system is undertaken on new systems, completely unknown systems or system with major repairs, where new and previous version of the system are not comparable (values of validations are not comparable). In systems without major changes, the initial validation is performed only once in the lifetime of a system. Initial validation is subdivided into prospective initial validation and concurrent initial validation.

6.5.3 Retrospective (annual) validation

The first retrospective validation is performed 12 months after the end of the initial validation period. It is a retrospective review of the collected data (no additional tests are required), repeated thereafter annually. The purpose of this review being to prove the adequacy of the maintenance and surveillance plan under the local operating conditions, the retrospective (annual) validation should include a report submitted to, and approved by, the person with overall clinical responsibility for dialysis.

Alternatively, the retrospective (annual) validation can be replaced by performing a continuous validation. When performing a continuous validation, a process for periodic audits (i.e. a process which inspects that the respective processes and procedures are established, still valid and followed) shall be implemented.

6.5.4 Revalidation

For an already existing water treatment system, which has been validated, Table E.2 provides guidance for revalidation. It is recommended that revalidation be carried out following

— any modification of the maintenance and surveillance plans (includes PQ as applicable),

— any modification of the system,

— changes in the requirements for dialysis fluid quality,

— changes in the feed water quality outside the accepted limits,

— changes to the disinfection frequency, and

— changes to the sampling frequency.

If the microbiological values are within the action levels and other values are below limit values, the system can be regarded as a validated system on the basis of the available data. The revalidation should include a report submitted to, and approved by, the person with the overall clinical responsibility for dialysis.

6.6 Monitoring and surveillance

This subclause describes the monitoring and surveillance activities to be conducted as part of the quality control and quality assurance process. Annex C provides further information on the surveillance guidelines for water treatment equipment, distribution systems and dialysis fluid. Guidance on parameters that should be subject to regular surveillance is provided in Table C.1.

Routine monitoring and surveillance should begin following the performance qualification (see 6.4) to ensure ongoing conformity with the dialysis water and dialysis fluid quality requirements set forth in Clause 4. Trend analysis of surveillance data should be used to provide advanced information on system performance, thus enabling a preventive rather than a reactive approach to system maintenance.

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

Fluid sampling for microbiological monitoring and surveillance should be performed before disinfection or 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. Samples for routinely scheduled microbiology surveillance should be obtained in the shortest possible time before the scheduled disinfection.

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. Clause 7 defines some of the surveillance activities to be performed at the dialysis facility as part of the quality assurance process. The microbiological surveillance methods described in 8.3 and Table 4 are intended to provide examples of acceptable methods. Other test methods, provided that they have been appropriately validated and are comparable to the methods cited in 8.3 and Table 4 can also be used. The frequency of monitoring or surveillance 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 programme can be found in Annex C. This guidance can also be used to supplement the manufacturer's recommendations.

As a water utility company's primary obligation is to provide the domestic user with water that meets the requirements of national or local drinking water regulations, the water company can introduce new methods of treatment or disinfection without prior notification to end users. Whilst the impact of any such change is unlikely to affect the domestic user, such changes can have an impact on dialysis providers and dialysis patients. In view of this, the dialysis provider should establish robust communications with the feed water supplier so that the supplier is aware that the water is used for the production of dialysis fluid [i.e. for life-saving treatment of end-stage renal disease (ESRD) patients]. The dialysis provider or clinic should also request that formal procedures be established in which the feed water supplier provides the clinic with correct and timely information about any changes in the supplied water quality (e.g. change of source or type of raw water treatment), in the chemicals or procedures used for the disinfection used by the feed water supplier or in the delivery (e.g. water supply interruptions). If such procedures cannot be established, additional monitoring or surveillance of feed water quality is highly recommended to maximize patient safety.

7.2 Surveillance of fluid quality

7.2.1 Surveillance of dialysis water quality

Dialysis water quality shall be monitored on a regular basis for the chemical and microbiological contaminants listed in 4.2.2 and 4.2.4. The surveillance schedule shall 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 the surveillance of chemical and microbiological contaminants in dialysis water are given in ISO 23500-3.

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 23500-3, the manufacturer's recommendations for surveillance may be followed for the manufacturer's recommended maximum period of use according to the instructions for use, provided that the system is operated under the validated conditions.

7.2.2 Surveillance of concentrate quality

Users are not required to test concentrates to demonstrate conformity with the requirements of ISO 23500-4 when using commercially available packaged chemicals intended for use in the preparation of liquid concentrates at a dialysis facility or when using commercially available liquid concentrates that are manufactured according to the requirements of ISO 23500-4. If the user prepares the concentrate from raw chemicals, the resulting concentrate should meet the requirements of ISO 23500-4.

7.2.3 Surveillance of dialysis fluid quality

Dialysis fluid quality shall be monitored on a regular basis for the microbiological contaminants listed in 4.4.2 Methods for the surveillance of microbiological contaminants in dialysis fluid are described in 8.3.

NOTE 1 Tests for bacterial growth and endotoxins are not required if the dialysis machine fluid pathway is fitted with a filter of an appropriate capacity to retain bacteria and endotoxins that is validated by the manufacturer and operated and monitored according to the manufacturer's instructions, unless the manufacturer requires such tests in the instructions for use.

NOTE 2 It is not possible to monitor conformity with the microbial quality requirements for substitution solutions (see Clause A.8).

As dialysis fluid is prepared from dialysis water and concentrates meeting the quality requirements of ISO 23500-3 and ISO 23500-4, 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 surveillance of chemical contaminants in the dialysis fluid is not required.

7.3 Surveillance of water treatment equipment

7.3.1 General

A brief description of the individual water treatment devices is provided in Annex B. Annexes C and G provide further information with respect to surveillance guidance for water treatment equipment, distribution systems and dialysis fluid.

7.3.2 Surveillance of sediment filters

There is no easy test to determine the effectiveness of a sediment filter; however, the 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 to avoid the development of an excessive pressure drop. The frequency of backwashing should follow the manufacturer's recommendations. Sediment filter surveillance 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 Surveillance 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, the 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 or above a specified value or at a predetermined interval. A log sheet should be developed to record the pressure drop measurements.

7.3.4 Surveillance of softeners

Softener surveillance consists of

— testing softened water for residual hardness,

— checking that the brine tank contains a sufficient supply of undissolved sodium chloride for automatically regenerating softeners, and

— checking that the timer indicates the correct time of day for time-controlled softeners.

The frequency of surveillance should be based on the hardness expressed either in terms of grains/gallon or in terms of calcium carbonate ($CaCO_3$) of the feed water and the capacity of the softener. When reverse osmosis is used, surveillance should be used to ensure that hardness limits established for the reverse osmosis membrane are not exceeded as calcium carbonate deposits form on the reverse osmosis membrane leading to a decline in product water quality and influence membrane life expectancy.

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 according to the manufacturer's instructions. Regardless of the method chosen, users should ensure that test accuracy and sensitivity are sufficient to satisfy the hardness surveillance requirements of the reverse osmosis system manufacturer when the softener is used as a pre-treatment 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 a 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 since it can clog orifices in the softener control head. The frequency of surveillance should be based on the length of the duty cycle (see Table C.1).

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 assessment of sufficient quantity of salt pellets according to manufacturer’s instructions should be recorded in a water softener log.

7.3.5 Surveillance of carbon media

If chlorine is not used in the feed water, the performance of the carbon bed is monitored by measuring the pressure drop across the carbon bed and by the carbon bed's time in use.

To mitigate possible risks, due to depletion of available valences in activated carbon, regular replacement of activated carbon shall be undertaken, even when chlorine breakthrough has not occurred. Replacement frequency is typically based on the manufacturer’s instructions or on activated carbon performance indicators (e.g. total organic compounds). Potential risks and dialysis treatment practices should be considered when choosing the frequency of replacement.

If small cartridge filters are used, the data sheet of the manufacturer regarding chlorine rejection capacity shall be observed.

If chlorine is used in the water entering the water treatment system (feed water), 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. The total chlorine level shall not exceed 0,1 mg/l. If the total chlorine level of water entering the water treatment system is below the permitted limit for treated water, additional measurements in the treated water are not necessary.

Testing for total chlorine should be performed at the time that the sample is drawn by appropriately trained personnel. Total chlorine measurement 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 according to the manufacturer's instructions. Whichever test system is used, it should have sufficient sensitivity and specificity to resolve the maximum levels described in 4.2.2 (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 surveillance can 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 surveillance should be based on the past performance of the system and on whether changes in feed-water quality have occurred.

The system should be flushed for a sufficient period of time to ensure that water sampled is representative of the water to be used for treatment. Sufficient flushing is necessary to ensure that sampled water does not been remain in the removal system between treatments, such that it would under-represent the chloramine level that would be delivered during normal operation. The minimum flush time should be 15 min unless otherwise directed by the manufacturer of the equipment. The analysis should be performed onsite since total chlorine levels will decrease if the sample is not assayed promptly.

The results of surveillance should be recorded on a log sheet.

7.3.6 Surveillance 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 proper preparation of the chemical, adequate mixing of the injected chemical with water flowing through the pre-treatment cascade, and reduction to a safe concentration level 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 when 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 their

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 shall be provided when chemicals for injection are prepared in a dialysis facility.

7.3.7 Surveillance 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 the rejection of solutes by the reverse osmosis membrane and to provide a measure of equipment performance. The percentage of rejection, *R*, is calculated using Formula (1):

$$R = \frac{\sigma_F - \sigma_P}{\sigma_F} \times 100 \quad (1)$$

where

σ_F is the feed water conductivity, in S/m;

σ_P is the permeate conductivity, in S/m.

Many reverse osmosis systems have a direct reading for percent 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 23500-3. 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 according to ISO 23500-3.

NOTE 1 For two-stage reverse osmosis systems, the percent rejection of the second stage will be lower than that of the first stage because of physico-chemical 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 the treated water's quality, surveillance of them can help ensure that the system is operating within the manufacturer's specifications and, thus, aids in maintaining the performance of the reverse osmosis membranes. Flow rates can be used to calculate the recovery percentage of the reverse osmosis system, *r*, as shown in Formula (2):

$$r = \frac{q_{v_P}}{q_{v_P} + q_{v_R}} \times 100 \quad (2)$$

where

q_{v_P} is the permeate volumetric flow rate;

q_{v_R} is the reject water volumetric flow rate.

NOTE 2 The percent 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.2.8). 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 D4516–19a (2019)[14].

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

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

— significant deviations are observed in the 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 a review of trends and its historic.

7.3.8 Surveillance 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 RO-treated water, chemical analyses to ensure that the requirements of 4.2.2 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 Surveillance of bacteria and endotoxin-retentive filters

The performance of bacteria and 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. Filters should be fitted with a means of evaluating filter integrity and fouling. One suitable method 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 surveillance can indicate when membrane fouling has progressed to the point that membrane replacement or cleaning is needed. Surveillance is also necessary to ensure that the device is being operated according to 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.

7.3.10 Surveillance of dialysis water storage and distribution

7.3.10.1 Surveillance of water storage tanks

For a system that distributes dialysis water to single-patient proportioning systems, routine surveillance of water storage tank for total viable microbial count and endotoxin concentration is generally accomplished indirectly by surveillance of the dialysis water at the first outlet to the distribution loop.

For routine surveillance of a storage tank that supplies dialysis water to a central dialysis fluid delivery system, or when direct surveillance 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 6.2) and a risk analysis of the likely impact of the change on system performance. All total viable microbial counts and endotoxin results should be recorded on a log sheet and should be subject to trend analysis.

7.3.10.2 Surveillance of the water distribution systems

Distribution piping systems used for dialysis water shall be monitored for total viable microbial count and endotoxin concentration to demonstrate the adequacy of the disinfection programme described in 8.2. The total viable microbial count and endotoxins shall not exceed the levels specified in 4.2.4 and Table 3.

Surveillance should be accomplished by taking samples from distribution loop and outlets supplying reuse equipment, bicarbonate mixing tanks and concentrate mixing tanks. Sample from the distribution loop is taken from a point prior to where the water returns to the reverse osmosis system or from the last outlet of each distribution loop. In case of multiple loops, each loop shall be sampled.

If the results of this testing are unsatisfactory, the disinfection programme should be re-evaluated and additional testing (e.g. endotoxin-retentive filter inlet and outlet, reverse osmosis product water, and storage tank outlet) should be undertaken as part of a troubleshooting strategy to identify the source of contamination, after which appropriate corrective actions can be taken.

Total viable microbial counts and endotoxin testing should be conducted on a regular schedule according to system validation data and 8.3. When a change has been made to an existing system, 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 6.2) and a risk analysis of the likely impact of the change on system performance. All bacteria and endotoxin results should be recorded on a log sheet to permit identification of trends and the need for corrective action.

7.3.11 Surveillance of bacterial control devices

7.3.11.1 Surveillance of ultraviolet irradiators

Ultraviolet irradiators intended for use as a direct means of bacterial control should be monitored for radiant energy output. UV irradiators equipped with radiant energy intensity sensors are available. Either a visual alarm or an output meter is acceptable for determining if the UV lamp is emitting sufficient radiant energy. UV irradiators should be monitored at the frequency recommended by the manufacturer. Given that radiant energy decreases with time, an annual lamp replacement is typically required. Periodic cleaning of the quartz sleeve can also be required, depending on water quality. A log sheet should be used to indicate that surveillance has been performed.

7.3.11.2 Surveillance of ozone generators

Ozone generators should be monitored for ozone output at a level specified by the manufacturer. The output of the ozone generator should be measured by determining the ozone concentration in the water at the most distal point from the ozone generator. A test based on indigo trisulfonate chemistry, DPD or an equivalent, or ozone-in-water test strips should be used to measure the ozone concentration. It is recommended that ozone concentration be measured each time disinfection is performed. An ozone-in-ambient-air test should be conducted on a periodic basis, as recommended by the manufacturer, to ensure conformity with standards for the permissible exposure limit. A log sheet should be used to indicate that surveillance has been performed.

7.3.11.3 Surveillance of hot water disinfection systems

Hot water disinfection systems should be monitored for temperature and time of exposure to hot water, as specified by the manufacturer. The temperature of the water should be recorded at the farthest point from the water heater; that is, where the lowest water temperature is likely to occur. It is recommended that the water temperature be measured each time a disinfection cycle is performed. A record that verifies successful completion of the heat disinfection should be maintained. Successful completion is defined as meeting the temperature and time requirements specified by the equipment manufacturer.

NOTE Subclauses 7.3.10 to 7.3.11 relate to and help explain Table C.1.

7.4 Surveillance of concentrate preparation

7.4.1 Surveillance of mixing systems

Systems for preparing either bicarbonate or acid concentrate from powder or other highly concentrated media at a dialysis facility should be monitored according to the mixing system manufacturer's instructions to ensure appropriate dissolution. If a facility designs its own system, it is considered as a manufacturer, requiring that verification, validation and surveillance procedures shall be developed and implemented in an equivalent manner to those of a manufacturer.

Acid and bicarbonate concentrates can be tested by measuring their conductivity, their density with a density meter or their specific gravity with a hydrometer according to the manufacturer's instructions. Although not required, some manufacturers of concentrate powder or other highly concentrated media may provide allowable ranges for either the conductivity, density or the specific gravity of concentrates prepared from their powder. The use of pH, alone, as an indicator of proper dissolution is inappropriate for both acid and bicarbonate concentrates because large variations in concentration do not produce significant changes in pH. Concentrates should not be used or transferred to holding tanks or distribution systems until all tests are completed. The test results and verification that they meet all applicable criteria should be recorded and signed by the individuals performing the tests.

7.4.2 Surveillance of additives

When additives are prescribed for a specific patient, the container holding the prescribed concentrates should be labelled with the name of the patient, the final concentration of the added electrolyte, the date and time when the prescribed concentrate was mixed and the name of the person who mixed the additive. This information should also be recorded according to the requirements of 4.5. The label should be affixed to the container when the mixing process begins.

7.5 Surveillance of concentrate distribution

A daily check to ensure that the appropriate acid and bicarbonate concentrate is connected to the corresponding concentrate delivery line is recommended if the storage tank is not permanently connected to its distribution piping.

Once a bicarbonate distribution system has been activated, dialysis fluid should be monitored weekly until sufficient data have been obtained to demonstrate the adequacy of the disinfection programme for the bicarbonate distribution system. The frequency of surveillance may then be reduced, but surveillance should be performed at least monthly. If elevated total viable microbial counts or endotoxin levels are found in the dialysis fluid, the disinfection programme for all systems involved in dialysis fluid preparation, including the bicarbonate concentrate distribution system, should be evaluated and revised. The frequency of surveillance should then be increased until it can be demonstrated that the revised disinfection programme is adequate to provide concentrate that allows preparation of dialysis fluid meeting the quality requirements of ISO 23500-5.

There are no published reports of acid concentrate supporting bacterial growth; therefore, it is not necessary to perform routine testing for total viable microbial count and endotoxins on those systems. However, it should be possible to disinfect these systems.

7.6 Surveillance of dialysis fluid proportioning

Dialysis fluid proportioning should be monitored following the procedures specified by the equipment manufacturer. When the user has specific requirements for surveillance of dialysis fluid proportioning, such as when dialysis machine settings are changed to allow the use of concentrates with a different proportioning ratio, the user should develop procedures for the routine surveillance of dialysis fluid electrolyte values, such as by surveillance of sodium (Na^+), potassium (K^+) or dialysis fluid conductivity.

8 Strategies for microbiological control

8.1 General

The strategy for controlling the proliferation of microorganisms in haemodialysis systems primarily involves appropriate system design and operation, and regular disinfection of the entire fluid system. This includes the reverse osmosis membranes (especially the clean side), the distribution piping, the inlet lines to the dialysis machines (located before the disinfection circuit of the dialysis machine) and the dialysis machines (which have their own disinfection circuit and programme). A key concept in ensuring conformity with the requirements of 4.2.4 and 4.4 is that disinfection schedules should be designed to prevent microbial proliferation, rather than to eliminate microorganisms once they have proliferated to an unacceptable level. With such a strategy, the surveillance levels of microorganisms and endotoxin demonstrate the effectiveness of the disinfection programme, rather than indicating when disinfection should be performed.

Microorganisms in fluids colonize surfaces resulting in biofilm formation, even when levels of microbial contamination are low. Microorganisms living within biofilms produce an extracellular polysaccharide or slime matrix, which protects them against disinfection. Microorganisms also excrete both simple and complex metabolites. Their effect on patients, and whether or not they are removed by endotoxin-retentive filters, is largely unknown. All strategies for microbial control of the system should, therefore, be proactive in order to limit microbial growth and biofilm formation, and prevent bio-fouling. It is of utmost importance that the disinfection procedure is applied from the start of the operation of the haemodialysis system as once formed, biofilm is difficult, if not impossible, to eradicate.

When the system is not used (e.g. during the night or on weekends), the stagnant dialysis water should be exchanged regularly (e.g. by performing rinsing cycles).

The combined efforts of disinfection and employing strategies for bacterial control make it possible to minimize microbiological growth and biofilm formation.

8.2 Disinfection

8.2.1 General

Disinfection is the only effective method of diminishing and inactivating microflora.

First, and most of all, the frequency of disinfection is important. Disinfection should be performed on a regular basis to limit biofilm formation and prevent bio-fouling within the fluid pathways of the system. Depending on the circumstances, different levels of disinfection can be required to comply with the fluid quality requirements of Clause 4.

Second, all surfaces in the circuit should be included in the disinfection procedure. This includes the reverse osmosis membranes (especially the clean side), the distribution piping, the inlet lines to the dialysis machines (located before the disinfection circuit of the dialysis machine) and the dialysis machines (which have their own disinfection circuit and programme).

Third, the disinfection procedure, when applied with a given frequency and with inclusion of all critical areas, should be capable of minimizing the effects of bio-fouling.

Disinfection can be performed using heat or chemicals. UV lamps can be used to inactivate planktonic cells but are of no value against any biofilm that has formed in the system.

8.2.2 Microbiological aspects of fluid system design

The circuit downstream of the reverse osmosis system, including the clean side of the reverse osmosis membranes, the distribution piping, tanks and filters in the distribution piping, and the inlet lines to the dialysis machines shall be maintained and disinfected so that it is possible to fulfil the microbiological requirements of ISO 23500-5 and ISO 23500-3.

EXAMPLE Good system designs include

— the use of a recirculation-type system,

— avoidance of dead ends and dead space areas,

— a high-quality finish to joints and connections,

— the use of materials compatible with the planned methods of disinfection, and

— avoidance of storage tanks; if a storage tank is necessary, it should be designed and constructed in such a manner that it can be cleaned and disinfected.

Once the water treatment system has been installed, water flow should be maintained to limit biofilm formation.

NOTE 1 Biofilm formation on a surface is a function of many factors including surface roughness and flow velocity. Experimental studies have demonstrated that turbulent flow in a piping system is able to minimize but not eliminate the formation of biofilm.

NOTE 2 In dialysis facilities, flow through the system is not always continuous since patients are not always treated overnight or the system can be undergoing maintenance. Consequently, it is not feasible to specify a minimum flow velocity that is effective in reducing biofilm formation and bacterial contamination. Furthermore, the use of such a flow velocity would not provide a substitute for regular disinfection of the distribution system.

The system design should also take into consideration preventive maintenance of the fluid distribution system, as well as education and training of staff in order to create awareness about disinfection and microbiological control.

The disinfection programme can compensate for a weakness in system design but will not totally prevent the formation of biofilm which, once formed, is difficult to eradicate.

8.2.3 Disinfection frequency

8.2.3.1 General

A key concept in ensuring conformity with the requirements of 4.2.4 and 4.4.2 is to design disinfection schedules to prevent the proliferation of bacteria, rather than to eliminate bacteria once they have proliferated to an unacceptable level (i.e. above the action level). With such strategy, the surveillance levels of bacteria and endotoxins serve to demonstrate that the disinfection programme is effective, rather than to indicate when disinfection should be performed.

A preventive disinfection strategy should be applied from the start. The disinfection frequency may be modified based on results obtained during validation, surveillance and revalidation activities. Any such modification should be appropriately documented. In contrast to manual disinfection, systems with automated disinfection allow the disinfection frequency to be easily adapted to changing requirements.

8.2.3.2 Dialysis water storage and distribution systems

Storage and distribution systems should be disinfected on a schedule that allows the water quality recommendations of 4.2.4 to be met routinely. For integrated treatment and distribution systems, the manufacturer's instructions for disinfection should be followed, provided routine surveillance shows that they are adequate to meet the requirements of 4.2.4. For systems assembled from individual components, the frequency of disinfection necessary to minimize biofilm formation varies according to the design of the system and, in the case of existing systems, according to the extent to which any bio-fouling has already occurred. Annexes C and H provide further information on surveillance of water treatment equipment and distribution systems. Annex D provides further information on strategies for microbiological control.

8.2.3.3 Concentrate mixing systems

Concentrate mixing equipment should be either

a) completely emptied, cleaned and/or disinfected according to the manufacturer's instructions, or

b) cleaned and/or disinfected using a procedure demonstrated by the facility to be effective in routinely producing concentrate that allows the recommendations of 4.3.1 to be met.

The mixing and disinfection data should be recorded for each mix and disinfection cycle using a dedicated log.

8.2.3.4 Concentrate distribution systems

Piped bicarbonate concentrate distribution systems should be disinfected either according to the manufacturer's instructions or using a procedure that has been demonstrated by the facility to be effective in routinely producing concentrate that allows the recommendations of 4.3.1 to be met. If the manufacturer does not supply disinfection procedures, the user should develop and validate a disinfection protocol. It is recommended that surveillance of concentrate distribution systems be performed on a routine basis.

When centrally produced bicarbonate concentrate is decanted into reusable concentrate containers, the containers and pick-up tubes should be disinfected at least weekly. Bicarbonate concentrate containers and concentrate pick up tubes should be rinsed with treated water, allowed to air-dry and stored in an inverted position at the end of each treatment day. As there are no published reports of acid concentrate supporting bacterial growth, the disinfection of acid concentrate distribution systems is not normally required. However, it should be possible to disinfect these systems.

8.3 Microbiological surveillance methods

8.3.1 General

The fluid system shall be routinely monitored in order to verify that the microbiological quality indicators (bioburden represented by total plate count and endotoxin concentration) are being met. An example of fluid diagram and corresponding microbiological quality is shown in Figure 2.

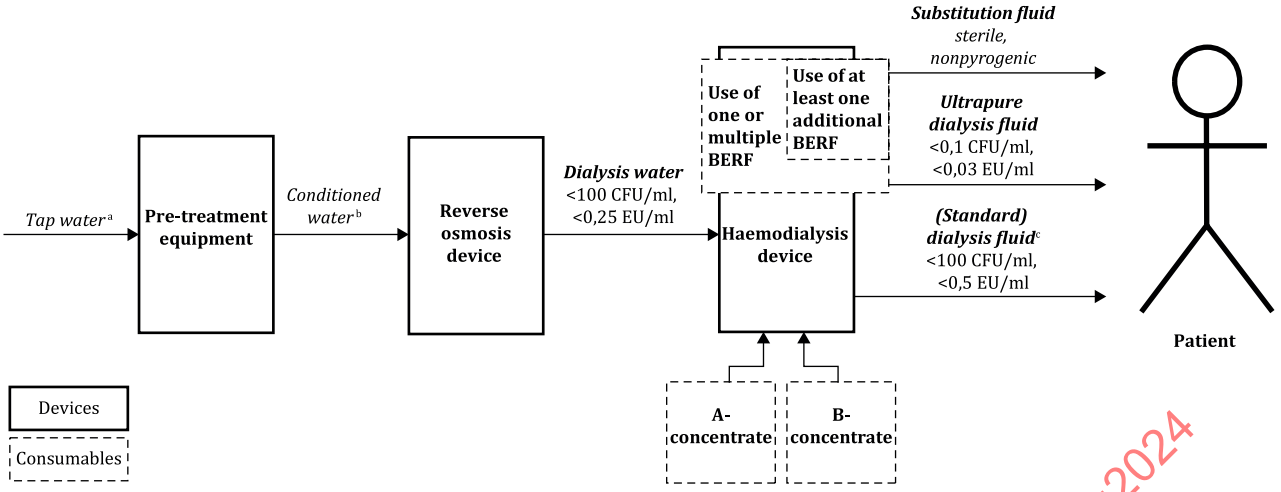
The frequency of sampling should meet applicable local recommendations. If no such recommendations exist, the following recommendation are given.

a) For the water treatment system, the number of samples and positions of sampling should be based on the complexity and size of the system. The frequency of sampling depends on the analysis of the data collected during the validation and revalidation activities. Monthly surveillance is most frequently adopted but less or more frequent surveillance may be possible based on data collected during the validations.

b) For dialysis fluid and haemodialysis machines without a validated bacteria and endotoxin-retentive filter, machines should be sampled on a regular basis to provide verification of the effectiveness of the disinfection process. The schedule of sampling will depend on the type of disinfection process being used. Each machine should be sampled at least once per year and different machines should be sampled on each occasion. Monthly surveillance is most frequently adopted.

c) For haemodialysis machines fitted with a validated bacteria and endotoxin retentive filter, and operated and monitored according to the manufacturer's instructions, it is not necessary to take samples of ultrapure dialysis fluid or substitution fluids unless required to do so to comply with the manufacturer's instructions for use (e.g. when the instructions for use specify the quality of the fluid entering the filter; see also Annexes C, D and E).

The results of testing should be subjected to trend analysis. When results exceed the action levels or in the case of a patient's pyrogenic reaction or suspected bacteraemia/fungemia, an investigation and follow-up should be initiated. This investigation can include additional sampling and extra disinfection procedures carried out as per the manufacturer's recommendations.



[a] Sometimes referred to as feed water or source water, is potable water meeting the requirements for drinking water.

[b] Water after pre-treatment. The quality of conditioned water shall meet the primary purification device's, in this case reverse osmosis device's, inlet water quality requirements.

[c] Typically, when ultrapure dialysis fluid is prepared, standard dialysis fluid is not used in a treatment.

Instructions for use of a devices (e.g. haemodialysis device) or consumables (e.g. dialysers, BERF filters) can specify stricter microbiological limit values, than those stated in this figure.

NOTE This figure shows an installation with a dialysis water preparation system with a reverse osmosis device as the primary water treatment method.

Figure 2 — Example of a fluid diagram and corresponding microbiological quality of a fluids

8.3.2 Sample collection

8.3.2.1 Dialysis water sample sites

Samples are to be taken at the outlets of the distribution system according to the sampling instructions provided by the manufacturer.

In the absence of manufacturer's instructions, the following may be used to ensure that the sample taken is not contaminated by any microbial growth at the point of sampling.

— Any hose attached to the sampling point should be removed. The exterior of the port should be disinfected with a sterile gauze or cotton swab wetted with 70 % isopropyl alcohol. Bleach or other disinfectant solutions should not be used. The sampling port is opened and fluid is allowed to run to waste for at least 60 s unless the port manufacturer instructions for use state otherwise, prior to the aseptic collection of the sample. The sample volume collected should be 5 ml to 1 000 ml depending upon the test to be run and/or as specified by the laboratory performing the test. The containers used for the samples to be cultured should be sterile and endotoxin free.

— Other sampling methods may be used provided they have been validated.

8.3.2.2 Dialysis fluid samples

Samples should be collected from the dialysis fluid line according to the sampling instructions provided by the manufacturer of the dialysis fluid delivery system. If not specified, the exterior of the sample port (not the lumen) may be disinfected with a sterile gauze or cotton swab wetted with 70 % isopropanol (isopropyl alcohol). Bleach or other disinfectant solutions should not be used. The sample should not be collected until all the alcohol has evaporated so as to leave no disinfectant residue in the sample.

The sample volume collected should be 5 ml to 1 000 ml depending upon the test to be performed and/or as specified by the laboratory performing the test.

Containers used for samples to be cultured shall be sterile and free of endotoxins.

NOTE Where the dialysis fluid delivery system is equipped with a dialysis fluid sampling port that can be accessed using a syringe, the sample port 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. If no sampling port is available and, if the dialysis machine permits it, samples can be collected immediately after the dialyser by disconnecting the effluent connector and aseptically collecting a "free/clean" catch sample after allowing dialysis fluid to run for at least 60 s.

8.3.3 Heterotrophic plate count

8.3.3.1 Storage of samples

Microbial analysis of any fluid sample should be conducted as soon as possible after collection to avoid unpredictable changes in the microbial population. Samples intended for colony counts should not be frozen but kept at a temperature of <10 °C until ready for shipping or collection by the laboratory. If samples cannot be analysed within 4 h of collection, they should be stored at <10 °C. Sample storage for more than 24 h should be avoided.

Storage of samples for endotoxin analysis may be different from what is given above, provided the complete procedure follows the manufacturer's instructions for use of the LAL assay.

8.3.3.2 Analytical methods

8.3.3.2.1 General

The recommended methods (e.g. membrane filtration, spread plate, pour plate), media and incubation ranges allow each dialysis center to develop a surveillance program appropriate to their facility.

The culture medium and incubation times selected should be based on the type of fluid to be analysed, e.g. standard dialysis fluid, water used in the preparation of standard dialysis fluid, ultrapure dialysis fluid, water used for the preparation of ultrapure dialysis fluid or fluid used for online therapies such as haemodiafiltration. The method selected should be based on the analysis of the advantages, disadvantages and sensitivity of each of the suggested methods. It should also ensure that the patient is provided with the necessary safeguards within any constraints imposed by local laboratory working practices and reimbursement.

8.3.3.2.2 Membrane filtration

Membrane filtration is filtration of the sample through a membrane filter with a pore diameter of 0,45 µm or less. Membrane filtration is a method used when the sample is to be concentrated to detect low levels of contamination (usually <1 CFU/ml) and can also be used for quantification of yeast and filamentous fungi should this be required. The volume to be filtered should be determined by the suspected level of contamination and should be between 10 ml and 1 000 ml.

Alternate membrane filtration techniques may be used provided that they have been appropriately validated and are comparable to the analytical methods outlined in this subclause.

8.3.3.2.3 Spread-plate technique

A pipette is used to apply 0,1 ml to 0,3 ml of a sample to a Petri dish (typically 90 mm in diameter) containing agar medium and spread over the surface of the agar. The detection limit of this technique is 5 CFU/ml when 0,2 ml of sample is used as the inoculum.

New methods can be developed in the future. Such methods may be used provided that they have been appropriately validated and are comparable to the analytical methods outlined in this subclause.

8.3.3.2.4 Pour-plate technique

A sample (typically 1 ml) is placed in a Petri dish and 15 ml to 20 ml of molten medium is added. The sample and medium are mixed carefully by gentle rotation and allowed to set. The time between addition of the sample and addition of the molten medium should not exceed 15 min. The plate is inverted and incubated. If 1 ml of sample is used, the detection limit of this technique is 1 CFU/ml.

Molten media should be <45 °C at the time the plate is poured.

New methods can be developed in the future. Such methods may be used provided that they have been appropriately validated and are comparable to the analytical methods outlined in this subclause.

8.3.3.2.5 Dip samplers

Currently available dip samplers are not suitable for use in dialysis applications.

8.3.3.3 Cultivation methods and conditions

The recommended methods and cultivation conditions can be found in ISO 23500-3, ISO 23500-4 and ISO 23500-5. The methodologies detailed use tryptone glucose extract agar (TGEA) or Reasoner's Agar No. 2 (R2A) incubated at 17 °C to 23 °C for a period of 7 d, or tryptic soy agar incubated at 35 °C for 48 h for the culturing of standard dialysis fluid and dialysis water. The rationale for the use of TSA and its inclusion is explained in ISO 23500-3:2024, Clause A.3.

Culture results obtained using the methods outlined are only a relative indicator of the bioburden and do not provide a measure of the absolute bacterial burden. Different media types and incubation periods can result in varying colony concentrations and types of microorganisms recovered[19]-[22].

R2A has been reported in previous studies to result in higher colony counts than tryptic soy agar (TSA) for dialysis water samples and dialysis fluids[23],[24]. The use of TGEA has also reported higher colony counts than TSA[25].

A publication by Maltais et al[26] considered whether culture of dialysis water and dialysis fluid using TSA-48 h can reasonably be considered "equivalent to" culture using TGEA-7 d or R2A-7 d. In the study, dialysis water and dialysis fluid samples were collected from 41 US dialysis programs between 2011 and 2014 and cultured at two US laboratories. Bacterial cultures were performed on 681 dialysis water samples (234 TSA-48 h and TGEA-7 d; 447 TSA-48 h and R2A-7 d) and 593 dialysis fluid samples (186 TSA-48 h and TGEA-7 d; 407 TSA-48 h and R2A-7 d). The proportions of samples exceeding the action level determined by the different methods were compared.

Zero bacterial growth in dialysis water was observed in

— 58,3 % (397/ 681) of samples based on the TSA-48 h method,

— 0 % (0/ 234) of samples based on the TGEA-7 d method, and

— 88,6 % (396/447) based on the R2A-7 d method.

Zero bacterial growth in dialysis fluid was observed in

— 64,4 % (382/593) of samples based on the TSA-48 h method,

— 0 % (0/186) of samples based on the TGEA-7 d method, and

— 95,1 % (387/407) based on the R2A-7 d method.

Paired comparisons of the number of samples of dialysis water and dialysis fluid with total colony counts at or above the action level of ≥50 CFU/ml by TSA-48 h versus TGEA-7 d and R2A-7 d was performed. The proportion of dialysis water samples yielding microbiological culture colony counts ≥50 CFU/ml by TGEA-7 d was significantly different from the proportion by TSA-48 h (p = 0,002; difference in proportion of 4,3 % [95 % Cl, 1,3 % to 7,3 %]). The proportion of dialysis fluid samples exceeding the action level by TGEA-7 d was not significantly different than by the TSA-48 h method (p = 0,69). A comparison of the proportions

of dialysis water and dialysis fluid using TSA-48 h and R2A-7 d methods did not demonstrate significant statistical differences.

Samples were not cultured using both TGEA-7 d and R2A-7 d, which would have allowed for a direct comparison of the commonly used methods, however such comparison already exists in Reference [24].

In view of the findings of this study, TSA has been included as a method for quantifying bacterial levels in dialysis fluid and dialysis water. It should be noted that, as these studies were performed on samples requiring compliance with standard dialysis fluid, TSA should only be used for such fluid and not for ultrapure dialysis fluid whose microbial contaminant level requirements are more stringent.

The culture medium and the assay method conditions selected should therefore be based on the type of fluid to be analysed; dialysis water, standard dialysis fluid, ultrapure dialysis fluid, and the purpose of the analysis. It should also ensure that patient safety is safeguarded and allow for consideration of local laboratory working practices, and that reimbursement requirements can be met.

Even with more sensitive techniques, conformity with the stringent requirement that online-prepared substitution fluid be sterile cannot be demonstrated by culturing; it has to be ensured by use of a validated process. Surveillance of the production of online-prepared substitution fluid will depend on the production system and should be performed according to the manufacturer's instructions (see Annex A).

8.3.4 Bacterial endotoxin test

Microbial endotoxins are assayed using the Limulus amoebocyte lysate (LAL) test based on the endotoxin-activated Factor C-mediated clotting cascade with lysate of blood cells (i.e. amoebocytes) from the Atlantic horseshoe crab. There are three methods for this test:

— the gel-clot technique, which is based on gel formation;

— the turbidimetric technique, which is based on the development of turbidity after cleavage of an endogenous substrate, and

— the chromogenic technique, which is based on the development of colour after cleavage of a synthetic peptide-chromogen complex.

Concern over the decline in the population of Atlantic horseshoe crab arising from its widespread use in bacterial endotoxin testing, has resulted in alternate approaches being developed. Factor C (FC) is one of the proteins naturally found in LAL and is the first enzyme in the clotting cascade. Factor C has been produced recombinantly (rFC) and together with a fluorescent marker forms the basis of an alternative to the classical approach based on the Atlantic horseshoe crab. This method is available from a number of commercial assay manufacturers and when compared to the LAL test, it has been shown to be as sensitive and reliable[27].

The commercial availability of this approach is also reflected in its inclusion in the European Pharmacopoeia (Ph. Eur.) <2.6.32>[75], the United States Pharmacopeia and the National Formulary (USP-NF)(<1085.1>)[77] and the Japanese Pharmacopoeia <G4-4-180>[79].

Endotoxin testing should be performed by fully trained personnel and follow applicable requirements and manufacturer's instructions.

NOTE When performing endotoxin testing, it is important to use the correct types of sample containers, labelled or validated for storage of endotoxin samples. Such containers are usually specified by the testing laboratory or the manufacturer of the test assay being used.

8.3.5 Determination of yeast and mould

Currently, there is no requirement for the routine surveillance for yeast and mould. If quantification of such species is required, Sabouraud or malt extract agar should be used with a 7-d incubation period at 20 °C to 22 °C. Alternate techniques validated against Sabouraud or malt extract agar with a 7 d incubation period at 20 °C to 22 °C may also be used, provided such methods are demonstrably comparable to the cited methods.

9 Location of and access to the water treatment system

The water treatment and storage system should be located in a secure locked area, accessible only by personnel authorized by the dialysis facility. An up-to-date list with contact details should be held centrally. Spare keys to the facility should be kept in a secure location.

The location for the water treatment system should be chosen with a view to minimizing the length and complexity of the distribution system. Access to the treatment system should be restricted to individuals responsible for surveillance and maintenance of the system.

The layout of the water treatment system should provide easy access to all components of the system, including all meters, gauges and sampling ports used for surveillance system performance. An area for processing samples and performing onsite tests is also recommended. Critical alarms, such as those associated with deionizer exhaustion or low water levels in a storage tank, should be configured to notify staff in the patient treatment area as well as in the water treatment room.

Water systems should include schematic diagrams that identify components, valves, sample ports and flow direction. Additionally, piping should be labelled to indicate the contents of the pipe and direction of flow. The use of text labels, such as “RO water”, and colour-coded “arrow tape” provides a convenient means of identifying the pipe content and flow direction. Sampling points should be marked as such and identified in schematic diagrams.

If water system manufacturers have not done so, users should identify major water system components and describe their function. How performance is verified and the actions to take in the event that the performance is not within an acceptable range should be readily available to the user.

10 Personnel

Policies and procedures that are understandable and accessible are mandatory, along with a training programme that includes quality testing, the risks and hazards of improperly prepared concentrate, and bacterial issues. Operators should be trained in the use of equipment by the manufacturer or should be trained using materials provided by the manufacturer. Additional training can be provided using materials from other sources. The training should be specific to the functions performed (i.e. mixing, disinfection, maintenance and repairs). A written record of training received should be kept for each operator and periodic audits of the operator’s conformity with procedures should be undertaken together with an ongoing training programme designed to maintain the operator's knowledge and skills.

Annex A
(informative)

Rationale for the development and provisions of this document

A.1 General

It has long been known that chemical and microbiological contamination of dialysis fluid places haemodialysis patients at risk of acute and chronic adverse events. From the beginning, it was recognized that there was a problem with including fluid quality requirements in a document directed at manufacturers of water treatment equipment or haemodialysis machines. Although a manufacturer can be responsible for providing equipment that, when assembled as a system, provides water, concentrate, or dialysis fluid that meets certain quality requirements, the manufacturer has no control over the equipment once it is installed.

For example, the treated water quality can change if a water treatment system is not well maintained or if there is some change in the municipal water feeding the system. Therefore, fluid quality standards were established independent of the standards for the equipment used to prepare those fluids. Since the day-to-day responsibility for maintaining fluid quality lies with the healthcare professionals at each dialysis facility under the direction of the facility's medical director, this document was prepared to provide guidance to those healthcare professionals on how to manage fluid preparation systems so as to comply with the requirements of the fluid quality standards.

A.2 Chemical contaminants

This clause provides the rationale for the requirements in 4.2.2.

ISO 23500-3 sets forth maximum levels of chemical contaminants for dialysis water in three groups:

— chemicals with documented toxicity in haemodialysis patients, such as aluminium[28]-[33], fluoride[34]-[37], nitrates[38], chlorine, chlorine by products and chloramine[39]-[47], lead[48]-[51],

— electrolytes normally included in dialysis fluid, and

— trace elements[52],[53].

The rationale for including particular chemicals and for setting their maximum levels, is set forth in ISO 23500-3:2024, Annex A.

Hazards to patients receiving haemodialysis treatment associated with the presence of organic compounds such as pesticides, polycyclic aromatic hydrocarbons and other chemical products present in the water are difficult to define. Consequences are probably of a long-term nature and routine measurement of such substances is difficult and costly. In view of this, no recommendation with respect to such compounds is made in this document.

The ability of water treatment systems to remove such compounds depends on the chemical structure and the concentration of the contaminant. Microfiltration and ultrafiltration are less effective than nanofiltration and reverse osmosis. Granular activated carbon (GAC) is on the other hand highly effective in removing such chemical contaminants. Compounds with a high degree of hydrophilicity may breach activated carbon faster than hydrophobic compounds. Backwashing cycles also play an important role in this process. Since granular activated carbons provide the primary method for the removal of chlorine and chloramine from the feed water, proper dimensioning of the carbon beds or filters is essential to ensure that the majority of the carbon valences are not already occupied limiting the removal of organic contaminants should there be a requirement to remove such compounds.

A.3 Microbiological contaminants

This clause provides the rationale for the requirements in 4.2.4.

ISO 23500-3 sets forth maximum levels of bacteria and endotoxins in dialysis water, along with action levels for these contaminants. The rationale for the maximum levels of bacteria and endotoxins is set forth in ISO 23500-3:2024, Annex A.

A.4 Requirements for concentrate

The rationale in this clause addresses the requirements in 4.3. Requirements for commercially available concentrates are given in ISO 23500-4. It was decided not to recommend limits on bacteria and endotoxins for concentrate prepared at a facility, even for bicarbonate concentrate. This decision was based on the difficulty of performing cultures and endotoxin assays in samples with high concentrations of salts. High concentrations of bicarbonate require special culturing techniques and are inhibitory in the LAL assay. It was determined that it was unreasonable to require an individual dialysis facility to meet the special conditions required for proper testing of bicarbonate concentrate and that patients would be adequately safeguarded by the quality recommendations for the water used to prepare the concentrate and for the final dialysis fluid. For users who wish to establish bacterial levels and endotoxin concentrations as part of a troubleshooting investigation, guidelines on performing cultures and endotoxin assays in bicarbonate concentrate are included in 8.3.3.3 and Clause A.10.

A.5 Microbiological contaminants in dialysis fluid

The rationale in this clause addresses the requirements in 4.4. ISO 23500-5 sets forth maximum levels of bacteria and endotoxins in three categories of dialysis fluid: standard dialysis fluid, ultrapure dialysis fluid and online-prepared substitution fluid. Where appropriate, action levels for bacteria and endotoxins are also given. The rationale for the maximum levels of bacteria and endotoxins is set forth in ISO 23500-5:2024, Annex A.

ISO 23500-3 sets a maximum allowable level for endotoxins in dialysis water of 0,25 EU/ml, while ISO 23500-5 sets a maximum allowable level for endotoxins in dialysis fluid of 0,5 EU/ml. The level for dialysis fluid is set higher than that for dialysis water in recognition that powder concentrates can contribute endotoxins, but not volume, to the final dialysis fluid. No such accommodation is made for bacteria since most bacteria will not survive in a viable form in powder concentrate.

A.6 Surveillance of carbon media

The rationale in this clause addresses the requirements in 7.3.5. Intensive surveillance of carbon beds is recommended because of the long history of adverse events related to chloramine contamination of dialysis fluid. Chloramine concentrations in municipal water can change from day to day and the capacity of carbon beds to remove chloramine can vary with the pH and temperature of the water, the nature of the chloramine compounds present and the presence of other substances in the water. The dependence of chloramine removal on multiple factors makes the performance of carbon beds unpredictable. Therefore, patient safety can only be ensured by intensive surveillance of the carbon bed performance.

Configuring carbon beds in series and sampling from a port located between the two beds provides one margin of protection against chloramine breakthrough. When chloramine is first detected in the effluent from the first bed, the second bed will still have some capacity for chloramine removal. This reserve capacity allows the user to conveniently replace the exhausted bed without risk to patients. The exhausted bed is discarded, the second bed is moved into the first position, and a new bed is placed in the second position. A new bed of virgin carbon should be used for replacement. Continuous surveillance with an online monitor provides the best protection of the patient. The online monitor should be capable of activating a means of diverting the water from the reverse osmosis system, for example by shutting down the reverse osmosis system, if the total chlorine level exceeds 0,1 mg/l.

In situations where chloramine is not used to disinfect the water and the ammonia level in the water is low, one carbon bed or a carbon cartridge filter with a shorter EBCT can be sufficient. Carbon cannot be

regenerated in a dialysis facility and the use of regenerated carbon is prohibited. Backwashing of carbon beds does not regenerate the carbon, although it can allow more efficient use of the bed's capacity by removing channels that can form in the bed during routine operation. The recommendation that the water purification system should operate for at least 15 min before samples of water from a carbon bed are drawn, is given to guard against inadvertently sampling water that has been in the bed for an extended period.

A.7 Strategies for microbiological control

The rationale in this clause addresses the requirements in Clause 8. Microbial growth within a fluid can occur in two forms: planktonic (i.e. freely existing in the bulk solution) and sessile (i.e. attached to a surface).

Biofilm formation occurs in a sequence of distinct events, including initial cell-to-surface or cell-to-cell attachment, microcolony formation, biofilm maturation and biofilm dispersal.

The ability of bacteria to produce extracellular matrix components that enable them to stick to surfaces and to each other is a prerequisite for biofilm formation. As the biofilm matures, the resident bacteria become embedded and protected in this self-produced extracellular matrix which is composed of polysaccharide, protein and DNA.

In view of this, no testing can show a complete picture of bacterial growth and the tests described and referred to in this document do not measure many microbial contaminants, including

— cell wall fragments from microorganisms,

— nucleic acids DNA and RNA, and

— metabolites of various kinds.

For this reason, a proactive disinfection programme should be used to combat bacterial growth in dialysis water and dialysis fluid systems.

A.8 Heterotrophic plate count

The rationale in this clause addresses the requirements in 8.3.3.

Sensitive culturing methods should be used to measure the low total viable microbial counts permitted for water used for haemodialysis applications. The membrane filter technique is particularly suited for this application because it permits large fluid volumes to be assayed. This technique increases the sensitivity of the method and the likelihood of detection of the bacteria present in low numbers. As the membrane filter technique is not always readily available in clinical laboratories, the spread plate assay or the pour-plate assay can be used as an alternative for water and standard dialysis fluid. If the spread plate assay is used, a calibrated loop should not be used to apply sample to the plate.

The sensitivity of an assay performed with a calibrated loop is low. A standard calibrated loop transfers 0,001 ml of sample to the culture medium so that the minimum sensitivity of the assay is 1 000 CFU/ml. This sensitivity is unacceptable when the maximum allowable limit for microorganisms is 100 CFU/ml. Therefore, when the spread plate method is used, a pipette should be used to place 0,1 ml to 0,3 ml of water or dialysis fluid on the culture medium. The pour-plate method may be used as an alternative method to the spread-plate method. If a sample volume of 1 ml is used, the detection limit of the pour-plate method is 1 CFU/ml.

Culture results obtained using any of the methods outlined in this document are only a relative indicator of the bioburden in dialysis water or dialysis fluid and do not provide a measure of the absolute bacterial burden. The original clinical observations on which the microbiological requirements were based used standard methods agar (SMA), a medium containing relatively few nutrients. Later, the use of TSA, a general-purpose medium for isolating and cultivating fastidious organisms was added. Several studies have shown that the use of nutrient-poor media, such as TGEA or R2A, results in an increased recovery of bacteria from water. Extending the culturing time up to 7 d and using incubation temperatures of 23 °C to 28 °C have also shown to increase the recovery of bacteria compared to incubation for 48 h at 35 °C to 37 °C[54].

The use of R2A and TGEA has been reported in some publications to result in higher colony counts than TSA for culturing of dialysis water samples and dialysis fluids[23],[24]. In a more recent publication,[26] no significant differences were indicated for the bacterial burden in the proportions of dialysis water and standard dialysis fluid yielding colony counts ≥50 CFU/ml when assayed using R2A and TSA at the conditions stated above. The study also demonstrated that when TGEA with TSA is used, the microbial burden in dialysis water and dialysis fluid used for standard dialysis treatment showed that the proportion of water samples yielding colony counts ≥50 CFU/ml incubated at 17 °C to 23° C for a period of 7 d was significantly different from the proportion established by TSA at an incubation temperature of 35 °C to 37 °C and an incubation time of 48 h (p = 0,001). The proportions of dialysis fluid samples in which microbial burden was ≥50 CFU/ml were not significantly different.

The authors suggested that the use of TSA balances the shorter time for actionable results with increased recovery compared to TGEA.

TGEA or R2A incubated at 17 °C to 23 °C for a period of 7 d, or tryptic soy agar incubated at 35 °C for 48 h are all validated and acceptable methods. The user should determine which of these methodologies is appropriate for the circumstance, taking into account the advantages of each. In doing so, the selection of the medium and the incubation times should also take into consideration the type of fluid to be analysed, for example:

— standard dialysis fluid,

— water used in the preparation of standard dialysis fluid,

— ultrapure dialysis fluid,

— fluid used for online therapies such as haemodiafiltration.

The method selected, should be based on the analysis of the advantages, disadvantages and sensitivity of each of the suggested methods. It should also ensure that the patient is provided with the necessary safeguards within any constraints imposed by local laboratory working practices and reimbursement.

When surveillance for microbial contamination in ultrapure dialysis fluid, the maximum allowable level of bacteria requires that culturing be performed using the membrane filtration method with a minimum of 10 ml of ultrapure dialysis fluid being passed through the filter. The use of larger volumes (up to 1 000 ml) will provide greater sensitivity, but the improved sensitivity needs to be balanced against the increased risk of contamination in collecting and handling the sample. Even with these more sensitive techniques, conformity with the stringent requirement that online-prepared substitution fluid be sterile cannot be demonstrated by culturing; it has to be ensured by the use of a validated process. The surveillance of the production of online-prepared substitution fluid depends on the production system and should be performed according to the manufacturer's instructions.

The culturing conditions recommended in this document can fail to identify the presence of some organisms. Specifically, the recommended methods do not always detect the presence of various non-tuberculous mycobacteria that have been associated with several outbreaks of infection in dialysis units[55]. Also, the recommended methods will not detect fungi and yeast, which have been shown to contaminate water used for haemodialysis applications[56].

The microbiological purity of packaged liquid concentrates and dry powder cartridges is the responsibility of the manufacturer. The surveillance of bicarbonate concentrate produced at a dialysis facility from powder and water, though not required routinely, may be undertaken as part of a troubleshooting investigation. The sodium content of TSA is sufficient for use in culturing bicarbonate concentrate without supplementation. Salt tolerance studies showed that optimal growth of organisms found in bicarbonate concentrate occurred when the sodium chloride concentration was approximately 3 % to 6 %[57]. Therefore, if a low-salt medium, such as Reasoner's 2A or TGEA, is used to monitor microbial contamination in bicarbonate concentrate, it should be supplemented by the addition of 4 % sodium bicarbonate.

A.9 Cultivation conditions

The rationale in this clause addresses the requirements in 8.3.3.3.

Due to cultivation of the samples, there is a delay between sampling and obtaining the results. If techniques are used that require seven days for the results to be available, significant contamination can be detected earlier than seven days when intermediate counts (e.g. every two days) are used.

A.10 Bacterial endotoxin test

The rationale in this clause addresses the requirements in 8.3.4. Bicarbonate concentrate inhibits the LAL assay. Inhibition is caused by the high concentration of solutes in the concentrate and by the pH. In the gel-clot assay, this inhibition results in a failure of the positive control to clot. In kinetic assays, inhibition results in a failure to recover the positive control to within −50 % to +200 % of the nominal value.

Dilution of the bicarbonate concentrate with water is the usual method for overcoming such inhibition. A minimum dilution of 1:16 is necessary; however, higher dilutions are recommended for more sensitive assays. A 1:20 dilution is recommended when using an assay with a sensitivity of 0,03 EU/ml as dilution reduces the detection limit of the assay. For kinetic methods, the sensitivity is the lowest concentration used to construct the standard curve. A kinetic assay is recommended because kinetic assays generally are more sensitive than gel-clot assays.

Standard gel-clot tests are incubated at 37 °C for the time recommended by the manufacturer. At the end of the recommended time, the tubes are inverted to detect the presence of a clot. A positive test will have a clot which will remain in the end of the tube as long as it is not shaken or bumped. A negative test will not have a clot and will tend to flow out of the tube when inverted. A clot that is semisolid and that flows slowly is classified as a negative clot. For example, when bicarbonate concentrate is tested using a gel-clot assay with a sensitivity of 0,03 EU/ml and the concentrate is diluted 1:20 (1,0 ml concentrate plus 19 ml LAL reagent water or equivalent), the positive control sample should clot, indicating that there is no inhibition of the assay. If the diluted bicarbonate concentrate sample clots, it indicates that the sample contains at least 0,6 EU/ml of endotoxins. Gel-clot assays with matched positive control, simplify testing and increase result reliability.

A.11 Emerging alternatives to heterotrophic plate count

A.11.1 General

The most commonly used method for monitoring microbiological quality for fluids used in haemodialysis and related therapies remains the heterotrophic plate count (HPC), a method that requires long incubation times. The validation and implementation of rapid and alternative microbiological methods has gained significant momentum over the past decade. Such methods which include flow cytometry (FCM), adenosine tri-phosphate (ATP) analysis and autofluorescence have been discussed in guidance documents issued by the Ph. Eur. <5.1.6>[76], the USP-NF <1223>[78] and the Japanese Pharmacopoeia on rapid microbiological methods (RMM)[80]. These emerging methods have seen only limited industrial and environmental application and there is no published data relating to their routine use for fluids used in haemodialysis and related therapies; their inclusion in this document is for informative purposes.

A.11.2 Flow cytometry

Flow cytometry is a commonly used technique to detect and measure physical and chemical characteristics of a population of cells or particles. It can also be used for the determination of bacteria in drinking water or the number of viable bacteria when combined with viability stains[58]. More recently, the technique was expanded towards creating flow cytometry fingerprints of bacterial communities to allow more detailed characterisation of such communities.[59],[60]

Whilst it has been suggested that FCM cell concentrations can replace HPC for routine water analysis due to the high level of information, accuracy, reproducibility and speed that the method offers[61], important challenges remain: difficulty in distinguishing between viable and non-viable bacteria, subjective data analysis and problems in dealing with bacterial aggregates and clusters.[61],[62]

A.11.3 Adenosine triphosphate bioluminescence assay

ATP quantification is able to demonstrate real time bacterial presence and ATP bioluminescence assays are available and have been used to assess the microbiological safety of surfaces in a clinical environment. However, it appears less precise for the low cell concentrations typically found in water. ATP measurements do not make the distinction between intra- and extracellular ATP, and this can significantly alter the results as, in certain biological matrices, the extracellular ATP concentration can be several orders of magnitude higher than the intracellular ATP concentration[63],[64]. Differences in species, cell sizes and physiological states can alter the ATP concentration per cell, making the conversion from ATP to biomass concentration difficult. Nevertheless, a small number of studies have applied the use of this methodology to evaluate the microbiological quality of water. Vital et al[65] compared cultivation-independent FCM and ATP analysis with conventional cultivation-based microbiological methods on water samples from two full-scale treatment and distribution systems, and showed that both methods were able to describe the microbiology of the systems accurately. Fulford et al[66] and Arroyo et al[67] suggested that the ATP test cannot at the present time be used as an alternative tool for presumptive assessment of the presence of microorganisms in water. On the other hand, Berney et al[68], suggested that ATP measurements presents an alternative way to assess the general microbial quality of drinking water as well as specific events that can occur during treatment and distribution, with equal application possibilities for the use of this approach in research and routine analysis.

A.11.4 Autofluorescence

The presence of endogenous autofluorescent molecules and metabolites within microorganisms permits the detection and quantitative enumeration of microcolonies or single cells[69]. Hand held fluorometers have been developed and their use forms the basis of some lab-on-a-chip platforms[70].

Annex B
(informative)

Equipment

B.1 General

This annex provides a brief description of the different components that can be included in systems to treat and distribute dialysis water and dialysis fluid, and to prepare and distribute concentrates for haemodialysis applications.

Two types of systems are used:

— systems in which dialysis water is distributed to a dialysis machine at an individual patient treatment station which prepares and controls the dialysis fluid for use at that station; and

— central dialysis fluid delivery systems, which prepare dialysis fluid centrally and supply it to multiple-patient treatment stations.

Since feed water quality and product water requirements can vary from facility to facility, not all of the components described in the following clauses will be necessary in every water treatment and distribution system. Also, not every dialysis facility will prepare concentrate at the dialysis facility.

Requirements for water treatment equipment used for haemodialysis and related therapies can be found in ISO 23500-2 and the requirements for equipment used to prepare concentrates at a dialysis facility can be found in ISO 23500-4.

Routine dialysis requires a well-functioning water treatment and distribution system, since dialysis cannot be performed without an adequate supply of water. In addition, certain components of the water treatment and distribution system are critical to its operation. An example of such a critical component is the circulating pump in an indirect feed system. A dialysis facility should develop contingency plans to cover the failure of its water treatment and distribution system or a critical component of that system. Such contingency plans should describe how to deal with events that completely prevent dialysis from being performed, such as failure of the facility's municipal water supply or electrical service following a natural disaster or water main break. Other plans should address how to deal with sudden changes in municipal water quality, as well as with failure of a critical component of the water treatment and distribution system. Similar contingency plans should be developed to deal with the failure of concentrate preparation systems.

B.2 Water treatment systems

B.2.1 General

Water treatment systems consist of a pre-treatment section that conditions the water supplied to the primary purification device, which can be followed by other devices that increase the final water quality. The pre-treatment section commonly includes a sediment filter, cartridge filters capable of retaining particles of various sizes, a softener and carbon beds. The primary purification process most commonly used is reverse osmosis, which can be followed by deionization and ultrafiltration for polishing the product water from the reverse osmosis system. The inclusion of a particular device in an individual water treatment system is dictated by local conditions.

Clause B.2 provides a brief description of the principal equipment used to purify water used in haemodialysis applications. Devices used to treat water for haemodialysis should comply with the requirements of ISO 23500-2, including certain design and performance specifications for individual water treatment devices.

General information is provided in B.2.2 to B.2.9. The design and instrumentation of individual water treatment devices can vary from these general descriptions. For example, softeners can be configured as a single resin bed that is regenerated outside the normal operating hours of the dialysis unit or they can have a dual-bed configuration that allows one bed to be regenerated while the other is used to provide water for normal dialysis operations.

Depending on the water supply quality and product water requirements, not every component in Clause B.2 is required in a given facility. Likewise, additional components can be required in certain circumstances. For example, carbon does not always provide adequate chloramine removal if the water contains substances, such as polyphosphates, that mask the reactive sites on carbon particles. In those circumstances, other processes, such as infusion of sodium bisulfite, can be required to obtain product water that meets the requirements of 4.2.2.

Users are encouraged to obtain detailed descriptions of all water treatment components, together with operating manuals and maintenance procedures, from the manufacturer or the supplier of the water treatment and distribution system.

B.2.2 Sediment filters

Permanent, backwashable sediment filters, also known as “bed filters”, are frequently located at or near the beginning of haemodialysis water treatment systems and are intended to remove relatively coarse particulate materials from incoming water. Although a single filtration medium may be used, bed filters known as multimedia filters are more commonly selected. These units contain multiple layers, each layer retaining progressively smaller particles. In this way, the bed is used to its fullest extent; the largest particles are removed in the first layer contacted by the water and the smallest in the final layer.

As the bed accumulates particulate material, open passages begin to clog and resistance to the water flowing through the filter increases. Ultimately, the increased resistance to flow will lead to a reduction in water supply to downstream components. To prevent this situation from occurring, bed filters are cleaned by periodic backwashing, which is accomplished either manually or by using a timer-activated control valve. Sediment filters should have an opaque housing or other means to inhibit proliferation of algae. Bed filters should be fitted with gauges to measure the pressure at the filters' inlet and outlet during use. These values can be used to determine the dynamic pressure drop across the filter (ΔP), which serves as an index of resistance to flow and provides a basis, together with the manufacturer's recommendations, for setting the frequency of backwashing.

B.2.3 Cartridge filters

Cartridge filters consist of a cylindrical cartridge of the filter medium with a central drainage core. The cartridge is contained within a filter housing with seals to separate the feed and product water streams. In the pre-treatment cascade, transparent filter housings can be useful because they allow any carbon or resin leakage to be seen without the need to break the integrity of the system. The housing can be cleaned to remove any algae growth when the filter cartridge is changed. For this reason, the use of opaque housings for cartridge filters is recommended, but not required. If transparent housings are used, they should not be exposed to natural light in order to minimize proliferation of algae. Cartridge filters should be fitted with gauges to measure the pressure at the filters' inlet and outlet during use. Although cartridge filters may be installed at the inlet to a water treatment system, their usual application is as a final filtration step prior to reverse osmosis. Resistance to flow through the filter increases as the cartridge accumulates particulate material, as indicated by an increase in ΔP. When the maximum ΔP recommended by the filter manufacturer is reached, the cartridge should be replaced according to the manufacturer's instructions.

B.2.4 Softeners

Water that contains calcium or magnesium can form relatively hard deposits and is called “hard water”. Water that has had these elements replaced by sodium ion exchange is called “soft water”, hence, the term “softener” is used. Softeners also remove other polyvalent cations, most notably iron and manganese, although they are somewhat limited in this regard. However, if significant concentrations of iron and manganese are present, special procedures should be implemented in order to reduce those concentrations to levels that do not interfere with the softening process or cause membrane fouling. The primary use of

softeners in haemodialysis water systems is to prevent hard water deposits from fouling reverse osmosis membranes.

A softener is a cylinder or vessel that contains insoluble spheres or beads, called "resin", to which sodium ions are attached. During operation, exchangeable sodium ions in the resin are progressively replaced by calcium and magnesium ions. When all the sodium ions have been used, the resin bed has reached a condition referred to as "exhaustion". Prior to exhaustion, softeners should be restored; that is, new exchangeable sodium ions are placed on the resin by a process known as "regeneration", which involves exposure of the resin bed to a highly concentrated sodium chloride solution. The concentrated sodium chloride solution is prepared in a separate brine tank, from which the solution is drawn during the regeneration process. A control valve on the softener regulates the regeneration and service cycles.

Automatically regenerated water softeners should be fitted with a mechanism to prevent water containing the high concentration of sodium chloride used during regeneration from entering the product water line during regeneration. For softeners with a time-controlled regeneration cycle, the face of the timer should be visible to the user. Operating controls should be positioned so as to minimize inadvertent resetting.

B.2.5 Carbon media

Carbon systems, often referred to as carbon filters, are the principal means of removing both free chlorine and chloramine. The removal of chloramine to a maximum level of 0,1 mg/l and the removal of free chlorine to a maximum level of 0,5 mg/l are necessary to protect haemodialysis patients from red blood cell haemolysis. In addition, free chlorine can also degrade some reverse osmosis membranes, depending on the membrane material. Determining the level of chloramine typically involves measuring both total chlorine and free chlorine, and assigning the difference in concentrations to chloramine. To permit a single test to be used, a maximum allowable level for total chlorine was set at the maximum allowable level for chloramine (0,1 mg/l).

In addition to removing free chlorine and chloramine, carbon also adsorbs a wide variety of other substances, including both naturally occurring and synthetic organic compounds. The capacity of carbon to remove free chlorine and chloramine can be reduced when other substances "mask" reactive sites on the carbon media. In addition, the rate of free chlorine and chloramine removal is reduced as the pH increases or as temperature decreases. The net effect of those variables is that the finite capacity of carbon beds to remove free chlorine and chloramine cannot be predicted with any certainty. Therefore, their performance needs to be monitored frequently.

Carbon systems should be adapted specifically to the maximum anticipated water flow rate of the system. When carbon is used for the removal of chloramine at a level of 1 mg/l or more, two carbon beds should be installed in a series configuration. A means should be provided to sample the product water from the first bed. A sampling port should also be installed following the second bed for use in the event of total chlorine breaking through the first bed. In situations where chloramine is not used to disinfect the water and the ammonium level in the water is low, one carbon bed or carbon cartridge filters can be sufficient. Exhausted carbon media should be discarded and replaced with new media, according to a replacement schedule determined by regular surveillance. For example, when testing between the beds shows that the first bed is exhausted, the second bed should be moved into the first position, the second bed should be replaced with a new bed and the exhausted bed should be discarded.

When samples from the first sampling port are positive for total chlorine, operation may be continued for a short time (up to 72 h) until a replacement bed is installed, provided that samples from the second sampling port remain negative. It was recognized that it is not always practical to rotate the bed positions in installations that use large, backwashable carbon beds. However, as there was concern that the capacity of the second bed can decrease unpredictably and thus no longer provide adequate backup if the first bed broke through, the replacement of both beds, if bed rotation is not possible, is recommended.

Granular activated carbon with an iodine number greater than 900 is considered optimal for chlorine/chloramine removal. When granular activated carbon is used as the medium for the removal of chloramine from water containing >1 mg/l chloramine, each bed should have an empty-bed contact time (EBCT) of at least 5 min at the maximum product water flow rate (a total EBCT of at least 10 min). Some water supplies such as those with a high organic content, can require alternative types of carbon that are more resistant to organic fouling. These types of carbon can have iodine numbers less than 900. When other forms of

carbon or granular activated carbon with an iodine number of less than 900 are used, the manufacturer should provide performance data to demonstrate that each bed has the capacity to reduce the total chlorine concentration in the water passing through the bed to less than 0,1 mg/l when operating at the maximum anticipated flow rate for the maximum time interval between scheduled testing of the product water for total chlorine. Regenerated carbon should not be used. Some granular activated carbons contain aluminium, which can elute from the carbon and add to the burden of aluminium to be removed by reverse osmosis or ion exchange. The use of acid-washed carbon minimizes this source of aluminium in the water.

Where practical, portable dialysis systems supplied with water known to contain chloramine should include two carbon beds in series, which together provide a 10 min EBCT. Where that is not practical, alternative technologies can be used, provided there is a redundant means of chloramine removal and that a total chlorine concentration of less than 0,1 mg/l is verified in a sample collected after the primary device before each treatment. Possible alternatives include:

— a granular activated carbon bed followed by a dense carbon block, and

— two carbon block filters in series.

Carbon beds used for free chlorine and chloramine removal are sometimes arranged as series-connected pairs of beds so that they need not be overly large. The beds within each pair are of equal size and water that flows through them are parallel. For removal of chloramine from water containing >1 mg/l, each pair of beds should have a minimum empty bed contact time of 5 min at the maximum flow rate through the bed. When series-connected pairs of beds are used, the piping should be designed to minimize differences in the resistance to flow from inlet and outlet between each parallel series of beds to ensure that an equal volume of water flows through all beds.

Although treatment of water by carbon is the method usually used to meet the requirement of 4.2.2 for total chlorine, it was recognized that, in certain situations, carbon does not always adequately remove chloramine. Inadequate removal of chloramine can occur when chloramines in the form of naturally occurring *N*-chloramines are present or when practices such as the use of high pH or the inclusion of orthophosphate or polyphosphates are used. If the pH of the incoming water is out of the range specified by the manufacturer, the carbon can malfunction and deplete rapidly. In other situations, such as acute dialysis with portable water treatment systems, it can be impractical to use the volume of carbon required to ensure adequate chloramine removal. In such circumstances, other strategies for chloramine removal can be needed to supplement carbon. Acid injection can be used to decrease pH (see B.2.6), anion exchangers (also known as organic scavengers) can be installed before carbon beds to remove organic matter and other substances that can foul carbon beds, and dealkalizers can be used to reduce alkalinity.

It is known that adding sodium bisulfite prior to the reverse osmosis system has been successful in eliminating chloramine in haemodialysis applications. Ascorbic acid has also been added to the acid concentrate used to eliminate chloramine from the final dialysis fluid. It should be noted that a minimum contact time is required for ascorbic acid to neutralize chloramine in water. If ascorbic acid is being used to neutralize chloramine and if unexplained red blood cell destruction or anaemia occurs, the effectiveness of the ascorbic acid neutralization of chloramine should be investigated. Other means of removing chloramine, such as redox alloy media and ultraviolet irradiation, are used in the pharmaceutical and electronics industries. These processes are currently being evaluated for haemodialysis applications. The final choice of a system for chloramine removal in haemodialysis settings depends on local conditions and can require the inclusion of more than one of the processes outlined above.

B.2.6 Chemical injection systems

Chemical injection systems can be used in the pre-treatment section of a water purification system to supplement the physical purification processes described in the previous clauses. Applications of chemical injection include the addition of sodium bisulfite to remove chloramine and the addition of acid to adjust the pH.

Chemical injection systems consist of a reservoir that contains the chemical to be injected, a metering pump and a mixing chamber located in the main water line. Chemical injection systems also include some means of regulating the metering pump to control the addition of a chemical. This system should be designed to tightly control the addition of the chemical. The control system should ensure that a chemical is added only when water is flowing through the pre-treatment cascade and that it is added in fixed proportion to the water flow

or based on some continuously monitored parameter, such as pH, using an automated control system. If an automated control system is used to inject the chemical, the controlling parameter should be independently monitored. There should also be a means of verifying that the concentrations of any residuals arising from the chemical added to the water are reduced to a safe level before the water reaches its point of use.

When acid is added to adjust pH, a mineral acid should be used; organic acids can act as a nutrient and allow bacteria to proliferate.

Reservations were expressed about the addition of chemicals to the water. However, it was recognized that the addition of chemicals can be necessary, in some circumstances, if a facility is to meet the maximum contaminant levels set forth in 4.2.2. For example, if the municipal water contains high levels of *N*-chloramines or chloramine in the presence of orthophosphate or polyphosphate, injection of sodium bisulfite can be one of the few options available for chloramine removal.

If chemical injection is used in the pre-treatment cascade, users should ensure that the addition of the chemical does not interfere with the operation of subsequent purification processes, including the primary purification process. For example, the performance of thin-film composite reverse osmosis membranes can be affected by the pH of the water supply. At pH levels below 7, the rejection of fluoride can be substantially reduced compared to its rejection at a pH of 8.

B.2.7 Ultrafiltration

Ultrafiltration (UF) and microfiltration (MF) are theoretically the best pre-treatment upstream reverse osmosis, removing from the water supply most of the potential elements responsible of membranes fouling such as particles, turbidity, bacteria and large molecular weight organic matter. Fouling of membranes remains a major issue and all effort should be made to reduce it. In order to maintain a constant output, fouling will cause an increase in the feed pressure which can only be addressed by increasing the frequency of cleaning. Therefore, controlling and limiting the deposits on the membrane will enhance the operating performance, reduce energy demands, increase membrane lifetime and have an overall positive effect on operating costs[71].

B.2.8 Reverse osmosis

RO systems have become widely used in haemodialysis water treatment systems, largely because these devices remove dissolved inorganic and organic solutes, as well as bacteria and bacterial endotoxins.

The following requirements apply to reverse osmosis systems.

a) When used to prepare water for haemodialysis applications, either alone or as the last chemical purification stage in a water treatment system, reverse osmosis systems should be shown to be capable, at installation, of meeting the requirements of ISO 23500-3 when tested with the water supply of the user.

b) Reverse osmosis devices should be equipped with online monitors that allow the determination of rejection rates and product water conductivity. The product water conductivity monitor should activate audible and visual alarms when the product water conductivity exceeds the preset alarm limit. The alarms should be capable of notifying staff in the patient care area when reverse osmosis is the last chemical purification process in the water treatment system. Monitors that measure resistivity may be used in place of conductivity monitors.

The RO membrane separation process components are a semipermeable membrane typically in a spiral-wound configuration, a pump, and various flow and pressure controls to direct the flow of water through the system. In operation, the water entering the RO module is pressurized by the RO pump and is then directed along the surface of the semipermeable membrane. A portion of the water is forced through the membrane, which is a process that removes inorganic and organic solutes, bacteria and bacterial endotoxins. The remainder of the water continues along the membrane surface and is directed to the drain. Water passing through the membrane is referred to as “product water” or “permeate”. The water that flows along the membrane surface and to the drain is known as “reject water” or “concentrate”. This flow configuration, known as “cross-flow filtration”, prevents a progressive build-up of materials on the membrane surface that would eventually lead to fouling and membrane failure. In some reverse osmosis systems, a portion of the reject water stream is recycled to the feed water stream. This recycling allows higher velocities across the

membrane surface which can help to reduce membrane fouling, as well as a higher overall use of water. RO systems can operate in a single-stage or two-stage (double-pass) configuration depending on feed water quality and/or local requirements and preferences. In a two-stage RO, the product water from the first stage acts as the water supply for the second stage.

NOTE The rejection rate of the second stage in a two-stage reverse osmosis system can be significantly lower than the rejection rate of the first stage. One reason for the difference in rejection rates is due to dissolved CO_2.

RO systems can also be fitted with flow meters, usually in the product water and the rejected water streams, to monitor the output of the RO system and gauges to monitor the pressure at various points in the system. Although not indicative of treated water quality, surveillance flow rates and pressures can help ensure that the system is operating within the manufacturer's specifications and thus will help ensure RO reliability.

In addition, it is recommended that, when a reverse osmosis system is the last chemical purification process in the water treatment system, means should be incorporated to prevent patient exposure to unsafe product water in the event of a product water conductivity alarm. Such means can include diversion of the product water to the drain, in addition to activating the audible and/or visual alarms that should be situated to ensure a prompt response by personnel in the patient care area.

Depending on membrane configuration and materials of construction, RO systems are sensitive to various feed water conditions that can lead to diminished performance or premature failure. To avoid such problems, users should carefully follow the manufacturer's instructions for feed water treatment and surveillance to ensure that the RO is operated within its design parameters.

A summary of the typical reverse osmosis rejection rate for the different type of contaminants (listed in Table 1) is presented in Table B.1. Table B.1 is not intended as an exhaustive compilation of all possible contaminants. Further information regarding the rejection coefficient for a specific compound by the membrane used may be available on request from the equipment or membrane manufacturer.

Table B.1 — Typical nominal rejection characteristics of thin film composite reverse osmosis membranes (adapted from Boccato et al, 2015)[71]

Class of contaminants	Contaminant	Typical RO rejection[a] %
Contaminants with documented toxicity in haemodialysis	Aluminium	96 to 99
	Copper	96 to 99
	Fluoride	92 to 99
	Lead	95 to 99
	Nitrate	90 to 95
	Sulfate	96 to 99
	Zinc	96 to 99
Electrolytes normally included in dialysis fluid	Calcium	93 to 99
	Magnesium	93 to 99
	Potassium	92 to 99
	Sodium	92 to 99
Other trace elements	Antimony	>90
	Arsenic	50 to 99
	Barium	99
	Beryllium	>90
	Cadmium	93 to 99
	Chromium	85 to 99
	Mercury	94 to 98
	Selenium	99
	Silver	93 to 97

[a] Average nominal rejection dependent on the overall water chemical profile and conditions (e.g. pH and oxidation status)/ different nominal rejection rates can be achieved depending on system configuration (e.g. double stage RO).

B.2.9 Deionization

Deionization (DI) is an ion exchange process that removes both anions (negatively charged ions) and cations (positively charged ions) from water. During the exchange process, hydroxyl ions replace other feed water anions, and hydrogen ions replace other feed water cations; the hydroxyl and hydrogen ions then combine to form pure water. DI systems can contain anion and cation resin in separate vessels, known as “dual-bed systems”, or can have both resin types mixed together in a single vessel, known as “mixed-bed sytems” or “unibed systems”.

Deionizers are an effective means of removing ionic contaminants from water. However, they do not remove non-ionic contaminants and they can contribute bacterial contaminants to the water rather than remove them. The inability of deionizers to remove non-ionic contaminants can limit aluminium removal by deionization, since aluminium is an amphoteric substance that changes from being cationic to being anionic as the pH varies from acidic to basic. At a neutral pH, aluminium is present mostly as colloidal aluminium which does not carry a charge and is not removed by deionization.

Furthermore, deionizers have a finite capacity for contaminant removal. Once the deionizer is depleted of hydrogen and hydroxyl ions, the next least avidly bound ions will be displaced by more avidly bound ions. For example, once the hydroxyl ions are depleted, anionic contaminants in the water will displace fluoride ions from the anion exchange resin. This phenomenon leads to high levels of fluoride in the product water, with subsequent patient injury and death[37]. Deionization, even in combination with an endotoxin-retentive filter, does not remove certain low-molecular-weight toxic bacterial products, such as microcystins. For the above reasons, the use of deionization as the primary means of treating water supplying multiple dialysis machines is strongly discouraged. Deionization may be used to polish product water from a reverse osmosis system or as a standby if the reverse osmosis system fails.

The most common configuration for DI is to have two mixed beds in series, with resistivity monitors being placed downstream of each bed. Upon exhaustion of the first bed, reliance for water of sufficiently high resistivity shifts to the second bed, and dialysis operations may be continued for a short time until a replacement bed is installed, provided that the product water from the second tank has a specific resistivity of 1 MΩ·cm or greater.

DI has a finite capacity that, when exceeded, will cause dangerously high levels of contaminants in the product water. Therefore, DI systems, when used to prepare water for haemodialysis applications, should be monitored continuously to produce water of 1 MΩ·cm or greater specific resistivity (or conductivity of 1 µS/cm or less) at 25 °C. An audible and visual alarm should be activated when the product water resistivity falls below this level and the product water stream should be prevented from reaching any point of use, for example by being diverted to drain. The alarm should be capable of notifying staff in the patient care area. Under no circumstances should DI be used when the product water of the final bed has a resistivity below 1 MΩ·cm.

The water supply for deionization systems should be pre-treated with activated carbon, or a comparable alternative, to prevent nitrosamine formation.

If a deionization system is the last process in a water treatment system, it should be followed by an endotoxin-retentive filter or another bacteria and endotoxin-reducing device. The tendency for deionizers to contribute bacterial contaminants to the water is greater when deionizers are kept as a backup for a reverse osmosis system, particularly if there is no flow through the deionizers. Some facilities counter this tendency by connecting the deionizers in parallel to the main water line and by maintaining a low flow through them. An alternative approach is to contract with a local supplier to provide backup deionizers on demand.

NOTE The requirements given above for deionization do not always apply to electro-deionization (EDI) technology, which can be used as an alternative to deionization following reverse osmosis in haemodialysis applications.

B.2.10 Bacteria and endotoxin-retentive filters

Bacteria and endotoxin-retentive filters are membrane-based separation devices that can be used to remove both bacteria and endotoxins. Bacteria and endotoxin-retentive filters should be placed in dialysis water systems at locations downstream of deionization. They may also be used at the end of the purification cascade and in dialysis water or central dialysis fluid distribution systems. Bacteria and endotoxin-retentive filters can also be used in the dialysis fluid line of individual dialysis machines as a final barrier against

bacteria and endotoxins. These filters are considered part of the dialysis machine and are not necessarily subject to all the recommendations that follow.

Endotoxin-retentive membranes used for haemodialysis applications are typically in either a spiral-wound or hollow-fibre configuration. Spiral-wound ultrafilters are usually operated in a cross-flow mode, with a fraction of the water supply being forced through the membrane and the remainder being directed along the membrane surface to drain. As with reverse osmosis, cross-flow filtration is intended to minimize membrane fouling. Hollow-fibre filters are typically housed in vessels similar to those used for cartridge sediment filters and can be operated in a cross-flow or a dead-end (no cross-flow) mode. When used in a water purification system for haemodialysis applications, an endotoxin-retentive filter should be shown to reduce the concentrations of bacteria and endotoxins entering the filter by factors at least as great as those specified in the manufacturer's labelling.

Bacteria and endotoxin-retentive filters should be fitted with a means of evaluating filter integrity and fouling during use. One suitable means is to monitor the pressure drop (ΔP) across the filter at a given product water flow rate using pressure gauges on the inlet (feed) and outlet (product) water lines. Alternatively, product water flow rate can be measured at a given pressure drop. Such surveillance will indicate when membrane fouling has progressed to the point at which membrane replacement or cleaning is needed. Surveillance also ensures that the device is being operated according to the manufacturer's instructions. Bacteria and endotoxin-retentive filters should be included in routine disinfection procedures to prevent uncontrolled proliferation of bacteria in the filter. If bacterial proliferation is not controlled, bacteria can "grow through" the membrane and contaminate the product water compartment of the filter. If the bacteria and endotoxin-retentive filter is operated in the cross-flow mode, a flowmeter should be fitted to monitor the flow rate of water being directed to the drain.

B.3 Dialysis water storage and distribution

B.3.1 General

The function of the water storage and distribution system is to distribute dialysis water from the treatment cascade to its points of use, including individual haemodialysis machines, proportioning systems used to prepare dialysis fluid centrally, dialyser reprocessing equipment and concentrate preparation systems. A water storage and distribution system typically contains a large volume of water exposed to a large surface area of piping and storage tank walls. As chlorine and chloramine are removed in the purification process, the water does not contain a bacteriostatic agent. This combination of circumstances predisposes wetted surfaces to bacterial proliferation and biofilm formation. Therefore, any dialysis water storage and distribution system should be designed specifically to facilitate bacterial control, including measures to prevent bacterial colonization and to allow for easy and frequent disinfection.

B.3.2 Water storage

When used, storage tanks should have a conical or bowl-shaped base and should drain from the lowest point of the base. Storage tanks should have a tight-fitting lid and be vented through a hydrophobic 0,22 µm to 0,45 µm air filter. The filter should be changed on a regular schedule according to the manufacturer's instructions or if it becomes wet. A means should be provided to effectively disinfect any storage tank installed in a water distribution system. Internal spray mechanisms can facilitate effective disinfection and rinsing of a storage tank.

B.3.3 Water distribution

Two types of water distribution systems are used: direct feed systems and indirect feed systems. In a direct feed system, dialysis water flows directly from the last stage of the purification cascade to the points of use. In an indirect feed system, dialysis water flows from the end of the purification cascade to a storage tank. From there, it is distributed to the points of use. The water storage and distribution system chosen for a particular situation should provide the simplest possible flow path and contain the smallest volume of water consistent with the operating needs of the dialysis unit. The simplest system is generally a direct feed system. However, direct feed systems can be impractical. For example, the pressure at the end of the purification cascade can be insufficient to provide adequate flow and pressure at the points of use without a booster

pump. If a direct feed system is used, it is also necessary to size the water treatment cascade to provide sufficient water to meet the peak demand. For these reasons, an indirect feed system with a storage tank can be used. Since storage tanks provide a large surface area for potential biofilm formation, their volume should be kept to a minimum in order to maximize water turnover in the tank. Whichever type of system is used, water distribution systems should be configured as a continuous loop and designed to minimize bacterial proliferation and biofilm formation (see Clause 8). A centrifugal pump made of inert materials is necessary to distribute the dialysis water and aid in effective disinfection. A multistage centrifugal pump is preferred for this purpose.

Direct feed distribution systems typically return unused dialysis water to the feed side of the reverse osmosis unit. If the pressure at the end of the distribution loop decreases to a value below the water pressure at the inlet to the reverse osmosis pressurizing pump, retrograde flow of untreated water into the distribution loop can occur. To minimize this risk, it is recommended that dual check valves or a break tank at the inlet to the reverse osmosis system with an air gap on the lines from the pre-treatment cascade and the distribution loop be used to prevent retrograde flow and that the pressure at the end of the distribution loop be monitored.

Distribution systems for dialysis water should be constructed of materials that do not contribute chemicals, such as aluminium, copper, lead and zinc, or bacterial contaminants to dialysis water. The choice of materials used for a water distribution system will also depend on the proposed method of disinfection. Table B.2 provides guidance on the compatibility of different materials and disinfection agents. Whatever material is used, care should be taken to select a product with properties that provide the least favourable environment for bacterial proliferation, such as smooth internal surfaces.

Table B.2 — Guidance on piping materials used in dialysis water distribution systems and their compatibility with common disinfectants

Material	Sodium hypochlorite (bleach)	Peracetic acid	Formaldehyde	Hot water	Ozone[a]
polyvinylchloride	X	X	X		X
chlorinated polyvinylchloride	X	X	X		X
polyvinylidene fluoride	X	X	X	X	X
cross-linked polyethylene	X	X	X	X	X
stainless steel		X	X	X	X
polypropylene	X	X	X	X	
polyethylene	X	X	X		X
acrylonitrile butadiene styrene		X			
polytetrafluoroethylene	X	X	X	X	X
glass	X	X	X	X	X

Key

X probable compatibility

[a] Ozone refers to ozone dissolved in water, not ozone gas.

Table B.2 is not intended as an exhaustive compilation of all possible compatible combinations of piping material and disinfectant. Considerations of compatibility should include any joint materials and pipe fittings, as well as the actual piping material. The concentration of germicide and the duration, frequency, and conditions (flow, pressure and temperature) of exposure should also be taken into account.

Users should verify compatibility between a given germicide and the materials of a piping system with the supplier of that piping system and/or the disinfectant supplier before using the germicide.

B.3.4 Bacterial control devices

B.3.4.1 General

Traditionally, chemical disinfection has been used to prevent bacterial proliferation in dialysis water storage and distribution systems. One consequence of the increased attention being paid to bacterial control in the dialysis water storage and distribution system is an interest in alternatives to traditional chemical disinfection, including ultraviolet irradiators, ozone generators and hot water disinfection systems. Both

ozone and hot water can allow more frequent disinfection of the dialysis water storage and distribution system because prolonged rinsing is not needed to remove residual disinfectant from the system before dialysis is recommenced. The use of ozone or hot water is possible only if the systems are constructed from appropriately resistant materials. This limitation applies not only to the piping and any storage tank that can be in the system but also to all pumps, valves and other fittings, including any O-rings and seals they can contain.

Ultraviolet irradiation can be used to kill planktonic cells but it has no impact on bacteria located in biofilm. In order to achieve an effective and preventive disinfection with the respective system, the user should refer to the recommendations given by the manufacturer of the device or system.

B.3.4.2 Ultraviolet irradiators

When used to control bacterial proliferation in dialysis water storage and distribution systems, UV irradiation devices should be fitted with a low-pressure mercury lamp which emits light at a wavelength of 254 nm and provides a dose of radiant energy of 30 mW·s/cm^2. If the irradiator includes a calibrated ultraviolet intensity meter, the minimum dose of radiant energy should be at least 16 mW·s/cm^2. The device should be sized for the maximum anticipated flow rate according to the manufacturer's instructions. Given the depth effectiveness limitations of UV irradiation and the resistance and repair ability of certain microorganisms to UV irradiation, water may be recirculated past the UV irradiator source multiple times to increase effectiveness. It is recommended that UV irradiators be followed by an endotoxin-retentive filter to remove pyrogens.

The recommendations provided in this subclause concern UV irradiator used specifically for bacterial control. UV irradiators may also be used for other applications in a water purification and distribution system.

Ultraviolet irradiation can also be used to control bacteria in the pre-treatment section of a water treatment system, such as the following carbon beds to reduce the bacterial burden presented to a reverse osmosis unit.

UV irradiators should be equipped with a calibrated ultraviolet intensity meter, as described above, or with an online monitor of radiant energy output that activates a visible alarm, which indicates that the lamp should be replaced. Alternatively, the lamp should be replaced on a predetermined schedule according to the manufacturer's instructions to maintain the recommended radiant energy output.

When ultraviolet irradiators are dipped in the storage tank to control bacteria, they should be designed to keep the required energy at the farthest position in the tank, considering the flow situation during operation.

B.3.4.3 Ozone disinfection systems

When used to control bacterial proliferation in dialysis water storage and distribution systems, an ozone disinfection system should be capable of delivering ozone at the concentration and for the exposure time specified by the manufacturer. When ozone disinfection systems are used, it is recommended that an ambient air ozone monitor be installed in the area of the ozone generator.

Bromate formation has been identified as a significant barrier in the application of ozone during water treatment for water sources that contain high levels of bromide. Bromate formation in dialysis water is influenced by factors such as bromide ion concentration, pH, the amount of ozone and the reaction time used to disinfect the water. Currently, there is no requirement to monitor for bromate. However, if bromide is present in the water supply, there should be awareness that the RO system removes only 93 % to 96 % of the inlet concentration, raising the possibility of low levels of bromate in the distribution loop if ozone is used to sanitize the system.

Ozone generators convert oxygen to ozone using a corona discharge or ultraviolet irradiation. The ozone is then injected into the water stream. An ozone concentration of 0,2 mg/l to 0,5 mg/l combined with a contact time of 10 min, measured at the end of the distribution loop, can kill bacteria, bacterial spores, viruses, moulds and yeast in water. The destruction of established biofilm can require longer exposure times and/or higher concentrations of ozone. Ozone can also degrade endotoxins.

Ozone can degrade many plastic materials, including PVC and elastomeric O-rings and seals. Therefore, ozone can be used for bacterial control only in systems constructed from ozone-resistant materials (see B.3.3).

B.3.4.4 Hot water disinfection systems

Thermal disinfection by hot water may be used to control microbial proliferation in dialysis water storage and distribution systems.

The time required to achieve a certain reduction of microorganisms at 80 °C, A_0, is expressed in seconds. Based on the specific temperature of the thermal disinfection cycle, it can be used for the quantification of heat disinfection between 65 °C to 100 °C (see ISO 15883-1)[6] as follows:

$$A_0 = \sum 10^{[(T-80)/z]} \times \Delta t$$

where

T is the temperature, in °C;

z is equal to 10 °C;

Δt is the selected time period, in s.

A value of A_0 = 600 kills most waterborne microorganisms like bacteria, including mycobacteria, fungi and inactivated heat-sensitive viruses. For thermoresistant bacteria, fungi or the inactivation of thermo-resistant viruses, a higher A_0 value is necessary.

Since the A_0 represents a combination of time and temperature, there are different ways to achieve the required value of A_0. For example, since an A_0 value of 1 is defined as an exposure to 80 °C for 1 s, A_0 of 600, can be achieved by a 10-min exposure at 80 °C, 1-min at 90 °C or 100-min exposure at 70 °C.

The water heater of the disinfection system should be capable of delivering hot water to any site in the dialysis water storage and distribution system at the temperature for the required exposure time to achieve the specified log reduction of microorganisms based on the thermal disinfection cycle.

The manufacturer's instructions for using hot water disinfection systems should be followed and disinfection should be performed at regular intervals from the date of commissioning the system. If no manufacturer's instructions are available, the effectiveness of the system can be demonstrated by validating that the system maintains a specified temperature throughout the system for a specified time and by performing ongoing surveillance with bacterial cultures and endotoxin testing.

Thermal disinfection using hot water, offers the user a variety of disinfection program options which include: distribution system only, RO membranes or integration of the inlet lines to the dialysis machines (located before the disinfection circuit of the dialysis machine). Complex systems will require a significant amount of energy to ensure that the effective temperature is maintained. Additionally, hot water disinfection systems can only be used in systems constructed from heat-resistant materials, such as polyvinylidene fluoride (PVDF), cross-linked polyethylene (PEX), stainless steel (SS), polypropylene (PP), and polytetrafluoroethylene (PTFE) (see B.3.3).

B.4 Concentrate preparation

B.4.1 General

Dialysis fluid is customarily prepared from two concentrates:

— the bicarbonate concentrate which contains sodium bicarbonate (and sometimes additional sodium chloride), and

— the acid concentrate which contains all remaining ions, acetic acid or citric acid, and sometimes glucose.

Some systems have also been developed that prepare acid concentrate from individual components, such as from a sodium chloride cartridge and a concentrated solution of the remaining minor electrolytes.

Acid concentrate can be supplied by the manufacturer in bulk or in single-use containers. In some cases, the manufacturer will pump the acid concentrate from bulk delivery containers into a holding tank at the dialysis facility. Systems have recently been introduced that allow a user at a dialysis facility to prepare acid concentrate from packaged powder and dialysis water using a mixer. If the acid concentrate is pumped into a bulk storage tank at the dialysis facility, the user is responsible for maintaining the concentrate in its original state and to ensure that the correct formula is used according to the patient's prescription. Acid concentrate prepared at the dialysis facility from powder and dialysis water is also the responsibility of the user.

Bicarbonate concentrate can be supplied by the manufacturer in one of the following three ways:

a) in powder cartridges that are used to prepare concentrate online at the time of dialysis;

b) as packaged powder that is mixed with dialysis water at the dialysis facility;

c) in single-treatment containers of liquid concentrate.

Dialysis fluid can also be prepared from a single concentrate that contains acetate, which is metabolized by the patient to yield bicarbonate. Acetate-based dialysis fluid is rarely used in routine clinical practice. In general, acetate-based concentrate is handled in a similar manner to that of acid concentrate, except that acetate-based concentrate systems use only one concentrate which is mixed with dialysis water. The labels of acetate-based concentrate are colour-coded white.

B.4.2 Compatibility of materials

All components used in concentrate preparation systems (including mixing and storage tanks, pumps, valves and piping) should be fabricated from materials (e.g. plastics or appropriate stainless steel) that do not interact chemically or physically with the concentrate to affect its purity, or with the germicides or germicidal procedure used to disinfect the equipment. The use of materials that are known to cause toxicity in haemodialysis, such as copper, brass, zinc, galvanized material, lead and aluminium, are specifically prohibited.

B.4.3 Labelling

B.4.3.1 General

Labelling strategies should permit positive identification by anyone using the contents of concentrate mixing tanks, bulk storage/dispensing tanks and small containers intended for use with a single haemodialysis machine. Requirements for such positive identification will vary among facilities, depending on the differences between concentrate formulations used and on whether single or multiple dialysis fluid proportioning ratios are used. The use of multiple dialysis fluid proportioning ratios in a single facility is strongly discouraged.

In addition to the container labelling described below, there should be permanent records of all batches of concentrate produced at a dialysis facility. These records should include the concentrate formula produced, the volume of the batch, the lot numbers of powdered concentrate packages, the manufacturer of the powdered concentrate, the date and time of mixing, any test results, the person performing the mixing, the person verifying mixing and test results, and the expiration date, if applicable.

Although it is the responsibility of facilities to develop and use labelling to positively identify the contents of mixing tanks, bulk storage/dispensing tanks and concentrate containers, the guidelines in B.4.3.2 to B.4.3.4 are suggested.

B.4.3.2 Mixing tanks

Prior to batch preparation, a label should be affixed to the mixing tank that includes the date of preparation and the chemical composition or formulation of the concentrate being prepared. This labelling should remain on the mixing tank until the tank has been emptied. Using a photocopy of the concentrate manufacturer's package label provides a convenient and comprehensive means of identifying the chemical composition or formulation of the concentrate; however, the lot number and expiration date should be marked out because they apply only to the dry powder.

B.4.3.3 Bulk storage/dispensing tanks

These tanks should be permanently labelled to identify the chemical composition or formulation of their contents. As with mixing tanks, bulk storage/dispensing tank labelling can be conveniently accomplished by affixing a copy of the concentrate manufacturer's package label.

B.4.3.4 Concentrate containers

Concentrate containers may be non-disposable vessels provided by haemodialysis machine manufacturers and having a capacity sufficient for one or two haemodialysis sessions. The extent of labelling for these containers depends on the variety of concentrate formulations used and on whether the facility uses dialysis machines with different proportioning ratios; the latter practice is strongly discouraged.

At a minimum, concentrate containers should be labelled with sufficient information to differentiate the contents from other concentrate formulations used at the facility. If a chemical spike is added to an individual container to increase the concentration of an electrolyte, the label should show the added electrolyte, the date and time added, and the name of the person making the addition (see B.4.5). The additional information may be simple or extensive, but in all cases, it should permit users to positively identify the container's contents.

Dialysis concentrates in canisters are usually intended for single use by the manufacturer and labelled accordingly. If not completely used, sometimes canisters are reused by the user. In those cases, the user is liable for any damage to health resulting from the reuse.

The following risks exist, among others:

— cross-contamination due to use of a contaminated canister contents with another patient, e.g. if the canister was not used for the same patient;

— effects arising from extended storage, e.g. beyond the next patient treatment day;

— content degradation or alteration if containers are not correctly resealed (e.g. contamination, evaporation and concentration of contents).

B.4.4 Concentrate mixing systems

B.4.4.1 General

Concentrate mixing systems require a source of dialysis water, a suitable drain and a ground-fault-protected electrical outlet. Protective measures should be used to ensure a safe work environment. For example, ventilation and personal protective equipment should be used to handle any residual dust that is introduced into the atmosphere as powdered concentrates are added to the system and to handle any additional heat produced by the device. Structural issues, such as the facility's weight-bearing capacity, should be addressed if systems are to be installed above ground level. Operators should at all times use appropriate personal protective equipment, such as face shields, masks, gloves, gowns and shoe protectors, as recommended by the manufacturer.

If a concentrate mixing system is used, the preparer should follow the manufacturer's instructions for mixing the powder with the correct amount of dialysis water. The number of bags or the weight of powder added should be determined and recorded.

The manufacturer's recommendations should be followed regarding any preventive maintenance and disinfection procedures. Records should be maintained indicating the date, time, person performing the procedure and results (if applicable).

B.4.4.2 Acid concentrate mixing systems

Acid concentrate mixing tanks should be designed to allow the inside of the tank to be completely emptied and rinsed according to the manufacturer's instructions when concentrate formulas are changed. Use of a tank with a sloping bottom that drains from the lowest point is one means of facilitating this process. As

concentrate solutions are highly corrosive, mixing systems should be designed and maintained to prevent corrosion. Acid concentrate mixing tanks should be emptied completely and rinsed with dialysis water before mixing another batch of concentrate. If another batch of concentrate is not to be mixed promptly, the mixing tank should be rinsed again with dialysis water before the next batch is mixed.

B.4.4.3 Bicarbonate concentrate mixing systems

Bicarbonate concentrate mixing tanks should be designed to drain completely; for example, they should have a sloping bottom and a drain at the lowest point. High-level and low-level alarms can prevent overfilling and air damage to the pump. As concentrate solutions are highly corrosive, mixing systems should be designed and maintained to prevent corrosion. Mixing tanks should have a tight-fitting lid and should be designed to allow all internal surfaces to be disinfected and rinsed. A translucent tank allows users to see the liquid level; the use of sight tubes is not recommended because of the potential for microbial growth, such as bacteria, algae and fungi.

Once mixed, bicarbonate concentrate should be used within the time specified by the manufacturer of the concentrate. The concentrate should be shown to routinely produce a dialysis fluid meeting the recommendations of 4.4.2. Overagitating or overmixing of bicarbonate concentrate should be avoided, as this can cause CO_2 loss and can increase the pH. (Systems designed for mixing dry acid concentrates can use methods that are too vigorous for dissolving dry bicarbonate.)

The mixing tank should be either

— completely emptied and disinfected according to the manufacturer's instructions, or

— disinfected using a procedure demonstrated by the facility to be effective in routinely producing a dialysis fluid that meets the recommendations of 4.4.2.

B.4.5 Additives

Manufacturers provide acid concentrates with a wide range of electrolyte compositions for different proportioning ratios. Most typical dialysis fluid prescriptions can be obtained by using one or more of these commercially available concentrates. If particular formulations are not available, manufacturers provide additives that can be used to adjust the level of potassium or calcium in the dialysis fluid. These additives are commonly referred to as “spikes”.

NOTE The use of additives is not approved in some countries.

Concentrate additives should be mixed with liquid acid concentrates according to the manufacturer's instructions, taking care to ensure that the additive is formulated for use in concentrates of the appropriate dilution ratio. When liquid additives are used, the volume contributed by the additive should be considered when calculating the effect of dilution on the concentration of the other components in the resulting concentrate. When powder additives are used, care should be taken to ensure that the additive is completely dissolved and mixed before the concentrate is used.

The use of concentrate additives such as potassium chloride in a canister is not recommended as, due to differences in density, homogeneous mixing is made more difficult. Furthermore, there is a risk of "island formation", i.e. areas with a high concentration of the concentrate additive. If the dialysis machine aspirates such areas, this can lead to a serious patient risk.

B.5 Concentrate storage and distribution

B.5.1 Compatibility of materials

All components used in concentrate distribution systems (including concentrate containers, storage tanks and piping) that contact the fluid should be fabricated from nonreactive materials (e.g. plastics or appropriate stainless steel) that do not interact chemically or physically with the concentrate to affect its purity. The use of materials that are known to cause toxicity in haemodialysis, such as copper, brass, zinc, galvanized material, lead and aluminium, are specifically prohibited.

B.5.2 Bulk storage tanks (acid concentrate)

Procedures should be in place to control the transfer of the acid concentrate from the delivery container to the storage tank to prevent the inadvertent mixing of different concentrate formulations. If possible, the tank and associated plumbing should form an integral system to prevent contamination of the acid concentrate. The storage tanks and inlet and outlet connections, if remote from the tank, should be secure and labelled clearly.

B.5.3 Distribution systems

B.5.3.1 General

Concentrate can be distributed from a central preparation point using reusable concentrate containers that contain sufficient concentrate for one to two treatments or it can be distributed through a piping system that provides concentrate connections at each treatment station. A combination of these two systems can also be used, with some concentrates distributed by concentrate container and others through a piping system. Two common configurations used for distributing concentrate through a piping system are gravity feed and pressurized. Gravity feed systems require an elevated tank, while pressurized systems deliver the concentrate using a pump and motor and do not require an elevated tank. The maximum allowable concentrate delivery pressure is specified by the manufacturer of the dialysis fluid delivery machine and should not be exceeded.

Elevated tanks are usually smaller than those used for preparing concentrates. Elevated tanks for bicarbonate concentrate distribution should be equipped with conical or bowl-shaped bottoms, tight-fitting lids, a spray mechanism, and high-level and low-level alarms. Any air vents should have 0,45 µm hydrophobic vent filters.

B.5.3.2 Acid concentrate distribution systems

Acid concentrate delivery piping should be labelled and colour-coded red at the point of use (at the container filling station or the dialysis machine connection). More than one type of acid concentrate can be delivered and each line should clearly indicate the type of acid concentrate it contains. Even though there are no published reports of acid concentrate supporting microbial growth, every effort should be made to keep the system closed to prevent contamination and evaporation. If the acid system remains intact, no rinsing or disinfection is necessary.

B.5.3.3 Bicarbonate concentrate distribution systems

Bicarbonate concentrate delivery piping should be colour-coded blue at the point of use (at the concentrate container filling station or dialysis machine connection). All joints should be sealed to prevent leakage of concentrate.

As bicarbonate concentrates provide excellent media for microbial proliferation, bicarbonate concentrate delivery systems should be disinfected on a regular basis to ensure that the dialysis fluid routinely achieves the level of bacteriological purity recommended in 4.4.2. The manufacturer's instructions can provide an initial disinfection schedule. However, this schedule can require adjustments for the user's bacteriological surveillance. For piped distribution systems, the entire system, including patient station ports, should be purged of bicarbonate concentrate before disinfection. Each patient station port should be opened and flushed with disinfectant and then rinsed; otherwise, it would be a “dead leg” in the system. Also, prompt use of bicarbonate concentrates prepared in dialysis facilities from powder and dialysis water is strongly recommended.

When reusable concentrate containers are used to distribute bicarbonate concentrate, they should be rinsed free of residual concentrate before disinfection.

All chemical disinfectants (e.g. sodium hypochlorite and peracetic acid products) that are compatible with dialysis machines can be used to disinfect bicarbonate concentrate distribution systems. However, some disinfectants attack biofilm better than others. Appropriate dwell times and concentrations should be used as recommended by the manufacturer of the concentrate system. If this information is not available, sodium

hypochlorite solutions, such as bleach, may be used at a dilution of 1:100 and proprietary disinfectants at the concentration recommended by the manufacturer for disinfecting piping systems. In the event that precipitation or salt build-up impedes flow through a piping system, cleaning with a 1:34 solution of 5 % acetic acid (e.g. distilled white vinegar) is recommended. Some manufacturers supply bicarbonate concentrate systems with UV irradiation or ozone systems for microbial control.

UV irradiation devices that are used to control microbial proliferation in the pipes of bicarbonate concentrate distribution systems should be fitted with a low-pressure mercury lamp that emits light at a wavelength of 254 nm and provides a dose of radiant energy of 30 mW·s/cm^2. The device should be sized for the maximum anticipated flow rate according to the manufacturer's instructions and be equipped with an online monitor of radiant energy output that activates a visual alarm indicating that the lamp should be replaced. Alternatively, the lamp should be replaced on a predetermined schedule according to the manufacturer's instructions to maintain the recommended radiant energy output. It is recommended that UV irradiators be followed by an endotoxin-retentive filter. Disinfection of the bicarbonate concentrate distribution system should continue to be performed routinely.

When used to disinfect the pipes of a bicarbonate concentrate distribution system, an ozone generator should be capable of delivering ozone at the concentration and for the exposure time specified by the manufacturer. When ozone disinfection systems are used, ambient air should be monitored for ozone according to national standards.

When heat is used to disinfect the bicarbonate distribution system, the time and temperatures used should be those recommended and validated by the manufacturer.

Over agitation or mixing of bicarbonate concentrate can result in loss of CO_2 from the solution. Loss of CO_2 results in an increase in pH and favours the formation of carbonate that can lead to precipitation of calcium carbonate in the fluid pathways of the dialysis machine following dialysis fluid proportioning.

B.5.3.4 Concentrate outlets

For piped concentrate distribution systems, each treatment station is equipped with a concentrate outlet for bicarbonate, one or more outlets for acid concentrate, and a dialysis water outlet for connection to the inlet line of the dialysis machine (optional). To prevent mix-ups with delivery of two or more types of acid concentrate, each concentrate should have its own outlet. Concentrate outlets should be compatible with the dialysis machine and have a means of minimizing the risk that the wrong concentrate will be connected to an outlet. The dispensing outlets should be labelled with the appropriate symbol (see Table B.3) indicating the proportioning ratio for the dialysis machine, if required, and should be colour-coded blue for bicarbonate and red for acid.

B.6 Dialysis fluid proportioning

Historically, dialysis fluid was buffered with acetate. For acetate-buffered dialysis fluid, dialysis water is mixed with an acetate-containing concentrate to produce the dialysis fluid. In such a system, the pH can vary depending on the supply water. Although a single concentrate is used to prepare acetate dialysis fluid, consideration should be given to checking both conductivity and pH because mix-ups involving acid concentrate and other chemicals can result in an acceptable conductivity with an incorrect pH.

One of the functions of the dialysis fluid is to correct metabolic acidosis present in patients undergoing dialysis treatment. With acetate buffered dialysis fluid, the acetate is converted by the body to bicarbonate, acetate intolerance can be present and is characterized by vasodilation and smooth muscle relaxation leading to hypotension.

In modern machines, dialysis fluid is produced by mixing two concentrate components, which may be provided as liquid or dry (powder) concentrates:

— the bicarbonate concentrate which contains sodium bicarbonate and sodium chloride, and

— the acid concentrate which contains chloride salts of sodium, potassium (if needed), calcium, magnesium, acetate (or citrate) and glucose (optional).

These two components are mixed simultaneously with purified water to make the dialysate.

Several types concentrates are available, with different ratios of acid concentrate to bicarbonate concentrate to dialysis water (see Table B.3). It is important that the acid and bicarbonate concentrates are matched with respect to the proportioning ratio, and with the model and setup configuration of the dialysis machine.

Generally, bicarbonate is available in one or two forms for each proportioning type (in liquid, cartridge or dry powder, and in various sizes). Each proportioning type has numerous acid concentrate formulations ("codes") with different amounts of potassium, calcium and magnesium ions, as well as glucose. To help differentiate between concentrates of different proportioning types, ISO 23500-4 recommends that the manufacturer include a geometric symbol on the labels, along with acid/base colour coding.

Table B.3 — Symbols and colour coding for different concentrate proportioning ratios

Concentrate type	Acid proportioning ratio[a] (red colour coding)	Geometric symbol	Bicarbonate concentrate (blue colour coding)	Comments
35X	1+34[a,b]	□ [Square]	Dry, liquid or cartridge	
36,83X	1+35,83[a]	○ [Circle]	Dry or liquid	Bicarbonate concentrate contains some NaCl.
45X	1+44[a,b]	△ [Triangle]	Dry, liquid or cartridge	
36,1X	1+35,1[a]	◇ [Diamond]	Cartridge	Powder cartridges can be used for other proportioning ratios except for 36,83X, in which the bicarbonate concentrate also contains NaCl.

NOTE An acetate-containing concentrate is colour-coded white.

[a] The acid mix proportions are expressed as the sum of the acid concentrate, the bicarbonate concentrate and the water mix proportions.

[b] The mix proportions 1:34 and 1:44 can be used instead of 1 + 34, and 1 + 44.

Different manufacturers of dialysis machines use different methods of controlling the proportions of the concentrates. Such control can be "fixed proportioning" or "servo-control". With both methods, the operator can select a desired sodium and bicarbonate level, or conductivities corresponding to defined sodium and bicarbonate levels, and the machine will make the necessary adjustments to achieve the selected levels. Both types use a redundant system of controls and surveillance. With fixed proportioning systems, the pumps are set to established volumes, and the final conductivity is verified. With servo-control machines, the individual concentrates are added until the conductivity achieves the expected value. A final redundant conductivity monitor monitors the conductivity. Some machines also monitor the pH of the dialysis fluid as an additional safeguard against gross errors in dialysis fluid formulation. A different type of machine with a batch tank and dedicated concentrates is also available.

Depending on the type of acidified concentrate in use, the acid component may be in the form of sodium acetate, sodium di-acetate or citric acid. Acetate is metabolized to bicarbonate in a 1:1 ratio, whilst citric acid generates bicarbonate in a 3:1 molar ratio.

When selecting the dialysis fluid bicarbonate, the physician should consider all sources of buffer delivered to the patient during the dialysis treatment, including the bicarbonate in the bicarbonate concentrate, the acetate, citrate or lactate in the acid concentrate which, when metabolized forms bicarbonate.

When selecting the bicarbonate prescription, the physician should consider the patient's nutritional status, assessed by history, physical examination, anthropometrics, serum albumin and protein nitrogen appearance, since individuals whose metabolism results in a small acid load are at higher risk of developing metabolic alkalosis following treatment. Decisions regarding the bicarbonate prescription should also take

into account changes in serum potassium, magnesium and calcium concentrations during dialysis, and the presence and severity of heart disease.

Some models of dialysis machines use a fixed proportionating ratio, whilst others can be set up or calibrated for use with concentrates of more than one proportioning ratio. (Note that changing from one proportioning ratio to another requires recalibration for some models of dialysis machines.) Thus, for such machines, the type of concentrate should be labelled on the machine or clearly indicated by the machine display. It is strongly recommended that facilities configure every machine to use only one type of concentrate.

Injuries related to incorrect dialysis fluid composition are rare, but they can and do happen when all procedures are not followed. Frequently, when the error occurs, several patients have been exposed before the facility recognizes the mistake. For example, because one of the concentrates is acidic and the other is basic, connecting the wrong concentrates to the machine can result in a dialysis fluid that can harm the patient. Thus, it is necessary for the operator to follow the manufacturer's instructions regarding dialysis fluid conductivity, including measuring the approximate pH with an independent method before starting the treatment of the next patient, if recommended by the dialysis machine manufacturer. More recently, systems have been developed that use three concentrates (a bicarbonate concentrate, a sodium chloride concentrate and an acid concentrate containing the remaining electrolytes) to allow more sophisticated variation of the dialysis fluid composition during dialysis.

B.7 Central dialysis fluid storage and delivery systems

B.7.1 General

Dialysis fluid may be prepared centrally and distributed to individual dialysis consoles at the treatment stations using a central dialysis fluid delivery system (CDDS). Central dialysis fluid delivery systems incorporate many of the features found in dialysis water storage and distribution systems (see Clause B.3) and concentrate preparation systems (see Clause B.4) and most of the recommendations in Clauses B.3 and B.4 are applicable to central dialysis fluid delivery systems; however, there are additional factors to be considered.

B.7.2 Design and maintenance

Central dialysis fluid delivery systems are usually designed as single-pass systems, although a distribution loop can also be used. If a distribution loop is used, it is necessary to pay attention to prevent calcium carbonate precipitation, an increase in pH resulting from loss of CO_2 and an increase in temperature as the dialysis fluid is circulated.

Central dialysis fluid delivery systems should be disinfected daily to limit biofilm formation using a chemical disinfectant or hot water. Such disinfection should include the tubing connection to the individual dialysis console.

Microbiological surveillance methods for central dialysis fluid delivery systems should be similar to that described in 8.3. Surveillance should include the individual dialysis consoles located at each treatment station, as well as the dialysis fluid distribution system. Sampling should include samples collected from the inlet to dialysis fluid proportioning system and the inlet to individual dialysis consoles. The frequency of surveillance should meet applicable local recommendations; if no such recommendations exist the following are suggested.

a) Water system: The number of samples and positions of sampling should be based on the complexity and size of the water system. The frequency depends on the analysis of the data collected during the validation and revalidation activities. Monthly surveillance is most frequently adopted but less frequent surveillance may be possible based on data collected during the validation and revalidation.

b) Dialysis fluid/haemodialysis machines without a validated bacteria and endotoxin-retentive filter: Machines should be sampled on a regular basis to provide affirmation of the effectiveness of the disinfection process. The schedule of sampling depends on the type of disinfection process being used. Each machine should be sampled at least once per year and different machines should be sampled on each occasion. Monthly surveillance is most frequently adopted.

c) It is not necessary to take samples of ultrapure dialysis fluid if their production paths are fitted with bacteria and endotoxin-retentive filters validated by the manufacturer and operated and monitored according to the manufacturer's instructions. It can be necessary to sample the dialysis fluid entering such bacteria and endotoxin-retentive filters depending on the manufacturer's instructions for use of the filters; for example, when the instructions for use specify the quality of the fluid entering the filter (see also Annexes C, D and E).

The results of testing should be subjected to trend analysis. When results exceed the action levels or in the case of a patient's pyrogenic reaction or suspected bacteremia/fungemia, an investigation and follow-up should be initiated. This investigation can include additional sampling and extra disinfection procedures carried out as per the manufacturer's recommendations.

B.7.3 Dialysis fluid storage

Central dialysis fluid delivery systems usually include a dialysis fluid storage tank. The tank should be designed to drain completely; for example, it should have a sloping bottom and a drain at the lowest point, and it should be ventilated through a hydrophobic 0,45 µm air filter.

B.7.4 Compatibility of materials

All components used in dialysis fluid storage and delivery systems (including storage tanks, pumps, valves and piping) should be fabricated from materials (e.g. plastics or appropriate stainless steel) that do not interact chemically or physically with the dialysis fluid to affect its purity, or with the germicides or germicidal procedure used to disinfect the system. The use of materials that are known to cause toxicity in haemodialysis, such as copper, brass, zinc, galvanized material, lead, and aluminium, is specifically prohibited.

Annex C
(informative)

Surveillance guidelines for water treatment equipment, distribution systems and dialysis fluid

C.1 Surveillance systems

Table C.1 provides guidelines on surveillance systems used for preparing and distributing dialysis fluid. The recommendations given in Table C.1 can be used as a starting point for developing a quality management programme for dialysis fluid when the manufacturer or supplier of the system does not provide adequate instructions. Not every item listed in Table C.1 will be required in all dialysis facilities and the frequency of surveillance can differ depending on the nature of the water supplied to the dialysis facility; for example, whether or not the water supply is disinfected using chloramine. The actual quality management programme for a given facility depends on the components used in that facility's water treatment system, the purposes for which the fluids are to be used and the results of validation procedures.

Table C.1 — Suggested framework for surveillance water treatment equipment, distribution system and dialysis fluid

Item to monitor	What to monitor	Typical range of values	Typical interval	Comments
Sediment filter	Pressure drop across the filter (see 7.3.2)	Pressure drop less than XXXX	Daily	NA
Sediment filter backwashing cycle	Backwash cycle timer setting (see 7.3.2)	Backwash clock set to XX:XX	Daily	NA
Cartridge filter	Pressure drop across the filter (see 7.3.3)	Pressure drop less than XXXX	Daily	NA
Water softener	Residual hardness of product water (see 7.3.4)	Hardness as specified by the manufacturer of the reverse osmosis equipment.	Daily	NA
Water softener brine tank	Level of undissolved salt in tank (see 7.3.4)	Salt level at XXX	Daily	NA
Water softener regeneration cycle	Regeneration cycle timer setting (see 7.3.4)	Regeneration cycle timer set to XX:XX	Daily	NA
Carbon beds	Product water total chlorine between the beds (see 7.3.5)	≤0,1 mg/l of total chlorine	Daily	Prior to each patient shift if chloramine is present in the water supply at 1 mg/l or more (see 7.3.5 for exceptions to these typical intervals). (Note that use of an online monitor can provide continuous surveillance and avoid the need for offline surveillance.)
Chemical injection system	Level of chemical in the reservoir, injector function, value of the controlling parameter (e.g. pH) (see 7.3.6)	Chemical level in reservoir ≥XXX; controlling parameter in range XX to XX	Daily (continuous surveillance is preferable)	NA

Key

NA not applicable

NOTE In this table, X is used as a surrogate for numeric values defined from the system operating and performance requirements.

It is not possible to specify universally acceptable operating ranges for each device listed in this table since some of the specifications will be system-specific. In those cases, the facility should define an acceptable operating range based on the manufacturer's instructions or measurements of system performance.

The actual interval for surveillance, testing, cleaning and/or disinfection should be based on the results of the validation process and ongoing trend analysis (see Clause 6, 7.2.3 and 8.2.3).

Table C.1 *(continued)*

Item to monitor	What to monitor	Typical range of values	Typical interval	Comments
Reverse osmosis	Product water conductivity, TDS or resistivity and calculated rejection (see 7.3.7)	$R \geq$ XX % $\sigma <$ XX µS/cm	Daily (continuous surveillance is preferable)	NA
Reverse osmosis	Product and reject flow rates, and calculated recovery (see 7.3.7)	$q_p \geq$X,X l/min XX % < $r <$ XX %	Daily (continuous surveillance is preferable)	NA
Deionizers	Product water resistivity or conductivity (see 7.3.8)	Resistivity ≥1 MΩ·cm $\sigma \leq 1$ µS/cm	Continuous surveillance	NA
Endotoxin-retentive filters	Pressure drop across the filter at a fixed flow rate, q_f, or product water flow rate, q_p, at a fixed pressure drop (see 7.3.9)	Pressure drop less than XXXX or flow rate greater than XXX	Daily	NA
Water system chemical contaminants	Chemical contaminants as listed in ISO 23500-3:2024, Tables 1 and 2	Maximums are as listed in Tables 1 and 2. The parameters to be monitored should be defined by the validation process on the basis of the expected contaminants.	Yearly	These recommendations apply to dialysis water. However, chemical analysis of the water supplied (or analysis results from the water supplier) is necessary to evaluate the overall performance of the water treatment system.
Dialysis water storage tanks	Microbial growth and endotoxins (see Clause 8)	Total viable microbial count is lesser than the action level (typically 50 CFU/ml); see 4.2.4 Endotoxin is lesser than the action level (typically 0,125 EU/ml); see 4.2.4	Monthly or as defined by the results of the validation process for storage tanks supplying a central dialysis fluid delivery system	Specific testing at this location is performed to troubleshoot contamination of the distribution system for tanks connected to a water distribution piping system until a pattern of consistent conformity with limits can be demonstrated.
Water distribution piping system	Microbial growth and endotoxins (see 7.4)	Total viable microbial count is lesser than the action level (typically 50 CFU/ml); see 4.2.4 Endotoxin is lesser than the action level (typically 0,125 EU/ml); see 4.2.4	Monthly or as defined by the validation process results	NA
UV irradiators	Energy output and/or the lamp life span (see 7.3.11.1)	Light output >XXX Lamp life span <XXXX	Monthly	NA
Ozone generators	Concentration in the water and contact time (see 7.3.11.2)	Ozone concentration >XXX Contact time >XXX Residual ozone after disinfection <X,XX mg/l	During each disinfection	NA
Hot water disinfection systems	Temperature and time of exposure of the system to hot water (see 7.3.11.3)	Temperature not less than XX °C; minimum exposure time at temperature ≥XX min	During each disinfection	This information can be available from the data logs of automated systems.
Chemical disinfection systems	Concentration of germicide in water and contact time	Germicide concentration >X,X mg/l; residual germicide concentration <X,XX mg/l after rinsing	During each disinfection	NA
Dialysis fluid	Conductivity, pH, electrolyte concentrations	XX,X mS/cm < $\sigma <$ XX,X mS/cm pH in the range 6,9 to 8,0 for dialysis fluid containing bicarbonate or as otherwise specified by the manufacturer	As specified by the manufacturer of the dialysis fluid delivery system (continuous surveillance for proportioning systems)	pH surveillance is necessary if recommended by the manufacturer of the dialysis fluid delivery system.

Key

NA not applicable

NOTE In this table, X is used as a surrogate for numeric values defined from the system operating and performance requirements.

It is not possible to specify universally acceptable operating ranges for each device listed in this table since some of the specifications will be system-specific. In those cases, the facility should define an acceptable operating range based on the manufacturer's instructions or measurements of system performance.

The actual interval for surveillance, testing, cleaning and/or disinfection should be based on the results of the validation process and ongoing trend analysis (see Clause 6, 7.2.3 and 8.2.3).

Table C.1 *(continued)*

Item to monitor	What to monitor	Typical range of values	Typical interval	Comments
Standard dialysis fluid	Microbial growth and endotoxin concentration in standard dialysis fluid (see 4.4.2)	Total viable microbial count is lesser than the action level (typically 50 CFU/ml); (see 4.4.2) Endotoxin level is lower than the action level (typically 0,25 EU/ml); (see 4.4.2)	Monthly, rotated among machines so that each machine is tested at least once per year and different machines are sampled on each occasion	The sample should be collected at the worst-case time (e.g. Monday morning) if possible.
Ultrapure dialysis fluid	Microbial growth and endotoxins in the ultrapure dialysis fluid as it enters the dialyser (see 4.4.3)	Total viable microbial count is lesser than the 0,1 CFU/ml; endotoxin is lesser than the 0,03 EU/ml (see 4.4.3) (see 8.3.1 and Annex E)	See NOTE.	NA
Substitution fluid	Microbial growth and endotoxins in the ultrapure dialysis fluid as it enters the dialyser (see 8.3.1 and Annex E)	Sterile and non-pyrogenic (see 8.3.1 and Annex E)	See NOTE.	NA

Key

NA not applicable

NOTE In this table, X is used as a surrogate for numeric values defined from the system operating and performance requirements.

It is not possible to specify universally acceptable operating ranges for each device listed in this table since some of the specifications will be system-specific. In those cases, the facility should define an acceptable operating range based on the manufacturer's instructions or measurements of system performance.

The actual interval for surveillance, testing, cleaning and/or disinfection should be based on the results of the validation process and ongoing trend analysis (see Clause 6, 7.2.3 and 8.2.3).

C.2 Cleaning/disinfection strategies

Cleaning/disinfection strategies for dialysis water treatment systems, dialysis water storage and distribution systems, concentrate distribution systems, and dialysis fluid distribution systems are given in Table C.2.

Prior to referring to the “typical interval” column, consult the manufacturer's instructions for more detail.

Table C.2 — Summary of cleaning/disinfection strategies for dialysis water treatment systems, dialysis water storage and distribution systems, concentrate distribution systems, and dialysis fluid distribution systems

Item for cleaning/ disinfection	Element(s) to be cleaned/disinfected	Cleaning/ disinfection	Typical interval	Comments
Reverse osmosis	The membrane module should be disinfected, paying particular attention to the product side (see 8.2.1).	Disinfection	Monthly or according to manufacturer's instructions (see Clause D.1)	The product side of the membrane is considered to be a part of the dialysis water distribution system. It should be disinfected at an interval sufficient to routinely produce dialysis water meeting the quality requirements of Clause 4. (See Clause D.1, third paragraph.) If needed, the feed side of the membrane should be cleaned periodically to remove foulants that can degrade membrane performance.
Dialysis water storage tanks	Tanks and pipes (see 8.2.3.2)	Disinfection	Monthly or according to manufacturer's instructions	More frequent disinfection can be necessary if indicated by microbiological testing results.
Dialysis water distribution piping system	Piping system (see 8.2.3.2, Clause D.1)	Disinfection	Monthly or according to manufacturer's instructions	More frequent disinfection can be necessary if indicated by microbiological testing results.
UV irradiators	Quartz sleeve (see 7.3.11.1)	Periodic cleaning (see 7.3.11.1)		
Concentrate mixing systems	Tanks and piping (see 8.2.3.3)	Cleaning and/ or disinfection		Disinfection is usually not needed for acid concentrate mixing systems.
Concentrate distribution systems (bicarbonate)	Tanks and piping (see 8.2.3.4, B.5.3.3)	Disinfection	Weekly (see Clause D.1, last paragraph)	If using sodium hypochlorite for disinfection, a concentration of 0,5 % to 1 % is recommended. If cleaning with acetic acid, a concentration of approximately 0,15 % acetic acid is recommended. (See B.5.3.3, fourth paragraph.) Disinfection is usually not needed for acid concentrate distribution systems.
Dialysis machine	System (see 8.2)	Disinfection	According to manufacturer's instructions	By its own disinfection circuit and programme. (See 8.2, third paragraph.)
CDDS	Dialysis fluid delivery system Individual dialysis console (see B.7.2)	Disinfection	Daily (see B.7.2)	Use chemical disinfectant or hot water. (See B.7.2, third paragraph.)
The actual interval for cleaning and/or disinfection should be based on the results of the validation process and ongoing trend analysis (see Clause 6 and 8.2.3).				

Annex D
(informative)

Strategies for microbiological control

D.1 General

The strategy for controlling the proliferation of microorganisms in haemodialysis systems primarily involves proper system design and operation, and regular disinfection of water treatment system and haemodialysis machines. A key concept in ensuring conformity with the requirements of 4.2.4 and 4.4 is that disinfection schedules should be designed to prevent microbial proliferation, rather than being designed to eliminate bacteria once they have proliferated to an unacceptable level. With this strategy, surveillance levels of bacteria and endotoxins serves to demonstrate that the disinfection programme is effective, not to indicate when disinfection should be performed. Gram-negative water bacteria, their associated lipopolysaccharides (microbial endotoxins) and nontuberculous mycobacteria (NTM), most frequently come from the community water supply and levels of those bacteria can be amplified depending on the water treatment system, dialysis fluid distribution system, type of dialysis machine and method of disinfection.

All components of dialysis water treatment and distribution systems, and dialysis fluid preparation and distribution systems, can serve as reservoirs of microbial contamination. Dialysis water distribution systems frequently use pipes that are of larger diameter and longer than are needed to handle the required flow. Oversized piping increases both the total fluid volume and the wetted surface area of the system. Gram-negative bacteria in fluids remaining in pipes overnight multiply rapidly and colonize the wet surfaces, thus producing microbial populations and endotoxin quantities in proportion to the volume and surface area. Such colonization results in the formation of protective biofilm that is difficult to remove once formed and that provides a barrier between the bacteria and germicide during disinfection.

Biofilm is a community of microorganisms consisting of cells that are irreversibly attached to a surface or interface or to each other. Biofilms can occur at solid-liquid, solid-air and liquid-air interfaces. Most microorganisms can form biofilms and more than 99 % of all microorganisms live in such aggregates. A feature of all biofilms is that the organisms are embedded in a matrix of microbial origin, consisting of extracellular polymeric substances (EPS), which comprises mainly polysaccharides and proteins, that coalesce to form hydrogel matrices. The structure of biofilm and the physiological attributes of biofilm organisms confer an inherent resistance to antimicrobial agents, whether those agents are antibiotics, disinfectants or germicides.

Mechanisms responsible for resistance can include

— delayed penetration of the antimicrobial agent through the biofilm matrix,

— altered growth rate of biofilm organisms, and

— other physiological changes related to the mode of growth of the biofilm.

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 bio-fouling. The key to avoiding bio-fouling is to minimize biofilm development. The extent of biofilm growth is dependent on the availability of nutrients. Classic biocidal approaches usually do not limit nutrient availability. In fact, some biocides increase nutrient availability by oxidizing recalcitrant organics and making them more bioavailable[72].

Routine disinfection should be performed to control microbial contamination of distribution systems. The frequency of disinfection will vary with the design of the system and the extent to which biofilm has already formed in existing systems. Sodium hypochlorite and ozone are generally the most effective agents against biofilm, and their use can be more efficacious if the pipes are treated first with a descaling agent. However,

in some cases, complete or partial replacement of a distribution system may be the only way to re-establish control over mature biofilm.

Maintaining flow through piping systems at all times has the potential to minimize biofilm formation, however a Reynolds number of 3 000 in a piping system can be insufficient to prevent biofilm.[73] [A Reynolds number of approximately 3 000 is obtained with a flow velocity of 0,15 m/s in a 2-cm of diameter pipe (0,5 ft/s in a 3/4" diameter pipe).]

Even if it were possible to specify a minimum flow velocity that was effective in reducing biofilm formation and microbial contamination, use of such a minimum flow velocity would not provide a substitute for regular disinfection of the distribution system. Other measures can also help protect pipes from contamination. A mechanism should be incorporated in a distribution system to ensure that disinfectant does not drain from pipes during the disinfection period. Dead-end pipes and unused branches and taps that can trap fluid should be eliminated because they act as reservoirs of bacteria and are capable of inoculating the entire volume of the system. Joints between sections of piping and between piping and fittings should be formed in a manner that minimizes the formation of crevices and other voids that can serve as sites for microbial colonization. Pipes should not be cut with a hacksaw. Any burrs should be removed before the joint is formed. These measures also minimize the possibility that pockets of residual disinfectant can remain in the piping system after disinfection.

A storage tank in the dialysis water or dialysis fluid distribution system greatly increases the volume of fluid and surface area available and can serve as a niche for water bacteria. Storage tanks are therefore not recommended for use in dialysis water or dialysis fluid distribution systems unless they are frequently drained and adequately disinfected. It can be necessary for the user to scrub the sides of the tank to remove microbial biofilm if the tank design and maintenance are not adequate to prevent microbial proliferation. A bacteria and endotoxin-retentive filter, distal to the storage tank, or some other form of microbial control device, is recommended.

For most haemodialysis machines, routine disinfection with hot water or with a chemical germicide connected to a disinfection port on the machine does not disinfect the line between the outlet from the dialysis water distribution system and the back of the dialysis machine. Users should establish a procedure for regular disinfection of this line. One approach is to rinse the haemodialysis machines with water containing germicide or hot water when the dialysis water distribution loop is disinfected. If this procedure is used with a chemical germicide, each haemodialysis machine should be rinsed and tested for the absence of residual germicide following disinfection.

Storage times for bicarbonate concentrate should be minimized (normally less than 24 h), as well as the mixing of fresh bicarbonate concentrate with unused portions of concentrate from a previous batch. The manufacturer's instructions should be followed if they are available. Facilities that reuse concentrate containers for bicarbonate concentrate should disinfect the containers at least weekly. Bicarbonate concentrate can support prolific growth of microorganisms. Containers and pick up tubes can be disinfected with household sodium hypochlorite solutions (300 mg/l to 600 mg/l free chlorine), with a contact time of about 30 min or according to another nationally approved standard, or according to the manufacturer's instructions.

The containers and pick-up tubes should be disinfected at least weekly. Following disinfection, the bicarbonate concentrate containers and concentrate pick up tubes should be rinsed with treated water, allowed to air dry and stored inverted at the end of each treatment day.

D.2 Microbial surveillance methods

D.2.1 General

The microbial quality of dialysis water is surveyed regularly to validate the effectiveness of the disinfection programme. The frequency of surveillance should be determined during the process of system validation. In the absence of a formal determination of frequency, surveillance is usually performed monthly. Surveillance can be accomplished by direct plate counts, in conjunction with the measurement of endotoxins.

Samples of dialysis water are collected from several places to give an indication of the microbial quality of the water throughout the dialysis water distribution system. For routine surveillance, samples should be collected from the last outlet of the dialysis water distribution loop, where dialysis water enters equipment used to reprocess dialysers, and where dialysis water enters equipment used to prepare bicarbonate concentrate or from the bicarbonate concentrate mixing tank. Additional testing, such as at the end of the water treatment cascade and at the outlet of the storage tank, if one is used, can be necessary during qualification of a newly installed system or when troubleshooting the cause of contamination within the dialysis water distribution loop. For central dialysis fluid distribution systems, samples should be collected from the last outlet of the dialysis fluid distribution loop.

For dialysis machines that are not fitted with validated endotoxin-retentive filters, dialysis fluid samples should be collected from enough machines so that each machine is tested at least once per year. For dialysis machines fitted with validated endotoxin-retentive filters, samples should be collected according to the filter manufacturer's instructions. If testing of any haemodialysis machine reveals a level of contamination above the action level, an investigation should be conducted. The investigation should be based on the presumption that other haemodialysis machines can also be contaminated. It should include a review of conformity with disinfection and sampling procedures and an assessment of microbiological data for the previous three months to look for trends. The offending machine should be re-tested and an additional sample of machines tested to determine if the contamination was limited to a single machine or more widespread. The person in charge should also be notified.

Cultures should be repeated when microbial counts exceed the allowable levels. If culture growth exceeds permissible standards, samples from the dialysis water distribution system or dialysis fluid distribution system and haemodialysis machines should be cultured weekly until acceptable results are obtained. Additional samples should be collected when there is a clinical indication of a pyrogenic reaction or septicaemia, and following a specific request by the clinician or the infection control practitioner.

Samples are always collected before sanitization/disinfection or no sooner than 24 h after disinfection. For systems disinfected daily, samples should be collected before, and as close as practicable to, the next disinfection. Samples from haemodialysis machines should always be collected before disinfection. Culture dialysis water and dialysis fluid weekly for new systems until a pattern has been established. For established systems, culture monthly unless a greater frequency is dictated by historical data at a given institution. If bio-fouling is suspected, for example due to erratic microbiological test results, checks for the presence of biofilm (see D.2.3) should be performed.

D.2.2 Sample collection

Samples are collected directly from sampling ports situated in different parts of the dialysis water or dialysis fluid distribution system. In general, the sampling ports should be opened and the dialysis water or dialysis fluid should be allowed to run for at least 60 s unless the sampling port manufacturer instructions for use state otherwise, before a sample is collected in a sterile, endotoxin-free container. Containers validated for collection of endotoxin samples should be used to collect samples. The sample volume collected should be 5 ml to 1 000 ml depending upon the test to be run and/or as specified by the laboratory performing the test. The exterior of the sampling ports should be disinfected with a cotton swab or sterile gauze wetted with 70 % isopropyl alcohol or as recommended by the port manufacturer. The sample should be collected only when no disinfectant residual is present.

Dialysis fluid samples should be collected from a sampling port in the dialysis fluid inlet line to the dialyser, or from the dialysis fluid outlet port of the dialyser, or from a sampling port in the dialysis fluid outlet line of the dialyser. In some newer haemodialysis machines, dialysis fluid flow stops when the dialysis fluid lines are disconnected from the port. In these instances, the machines are equipped with dialysis fluid sampling ports that can be accessed using a syringe. The exterior of the sampling ports should be disinfected with a cotton swab or sterile gauze wetted with 70 % isopropyl alcohol, and allowed to air dry or as recommended by the manufacturer. A sterile syringe should be used to aspirate at least 10 ml of dialysis fluid out of the sampling port and be discarded. A new appropriately sized sterile syringe should be attached and used to draw the sample. The sample volume collected should be 5 ml to 1 000 ml depending upon the test to be run and/or as specified by the laboratory performing the test.

Containers used for samples to be cultured should be sterile and endotoxin free.

D.2.3 Heterotrophic plate count

Samples should be analysed as soon as possible after collection to avoid unpredictable changes in the microbial population. If samples cannot be analysed within 4 h of collection, they should be stored at <10 °C without freezing and during transit to the laboratory. Sample storage for more than 24 h should be avoided.

The reference method for culturing is the membrane filtration technique. With this method, a known volume of sample or diluted sample is filtered through a 0,45 µm membrane filter and the membrane filter is aseptically transferred to the surface of an agar plate. The spread-plate technique may also be used. With this method, an inoculum of at least 0,1 ml of sample is spread equally over the surface of the agar plate. The use of a calibrated loop to apply the sample to the agar plate is not permitted. The pour-plate technique may also be used. A sample volume of 0,1 ml to 0,3 ml is usually used with this method. Dip samplers should not be used. The culture medium used should be selected based on the type of fluid to be analysed, for example the standard dialysis fluid, water used in the preparation of standard dialysis fluid, ultrapure dialysis fluid, water used for the preparation of ultrapure dialysis fluid or fluid used for online therapies, such as haemodiafiltration. Blood and chocolate agars should not be used.

Validated media, incubation times and temperatures are specified in ISO 23500-3, ISO 23500-4 and ISO 23500-5. During incubation, the plates can be sealed or kept in a plastic bag to avoid desiccation of the agar if that is a concern, e.g. for methods requiring 7-day incubation. Colonies should be counted using a magnifying device. If a more accurate count from plates containing fewer than 30 colonies or more than 300 colonies is desired, larger or smaller volumes may be cultured. Smaller volumes can be obtained by making 1:10 serial dilutions in sterile phosphate buffer. If larger volumes are required, the membrane filtration method should generally be used.

Heterotrophic plate counts do not provide a good measure of the presence of biofilm. Fluid samples give no information about the site, extent or composition of a biofilm. Although biofilms contaminate the fluid in a distribution system, they do so only very irregularly. Erratic colony counts can indicate the presence of bio-fouling since clusters of cells may be sloughed from the biofilm with release of bacteria into flowing fluid. Currently, few practical methods are available for the routine detection of biofilm. Conventional methods rely on sampling-defined surface areas or on exposure of test surfaces (coupons) with subsequent analysis in the laboratory. A classic example is the so-called "Robbins device", which consists of plugs inserted flush with pipe walls, thereby experiencing the same shear stress as the wall itself. After given periods of time, they are removed and analysed in the laboratory for biofilm-relevant parameters[74]. If careful attention is paid to routine disinfection, routine surveillance for biofilm is not necessary. However, when the level of biofilm leads to a bio-fouling situation, it can be necessary to determine the level of biofilm in the system using the methods currently available.

D.2.4 Endotoxin test

Endotoxin testing is performed using the LAL assay. A variety of different assay methods are available and a number of new methods are in development. Existing available methods include gel-clot, which is semi-quantitative, kinetic, which are chromogenic, turbidimetric or end point.

The gel-clot LAL assay is not as sensitive as the kinetic assay and provides only a positive or negative result; that is, it shows if endotoxins are present, or not, at a particular concentration. Single-tube gel-clot tubes are available from several commercial sources, and kits with the typical following sensitivities available: 0,015 EU, 0,03 EU, 0,06 EU, 0,125 EU, 0,25 EU and 0,5 EU. At a minimum, two tubes should be run each time the assay is performed. The first tube contains LAL reagent and the sample to be tested. The second tube contains LAL reagent, a known amount of endotoxins and the sample to be tested. The second tube acts as a positive control to confirm the absence of any interference that can lead to a false-negative result. Positive control tubes are available from the suppliers of commercial LAL assays.

The kinetic LAL assay uses control standard endotoxins to generate a standard curve to which unknowns are compared and concentrations are determined using linear regression. The kinetic assays employed in laboratories generally use a computer-driven spectrophotometer that automatically calculates the amount of endotoxins on the basis of colour development, turbidimetric readings or onset times for gel formation.

Apart from the LAL test, a number of assays with varying specificities and sensitivities are available to quantify and define biologically active substances of microbial origin (e.g. silkworm larvae, mononuclear cell cytokine assay and 1,3-β D-glucans).

D.3 Interpreting the results of microbial surveillance

D.3.1 Dialysis water

Microbial surveillance or culture results are dependent upon three basic parameters: culture medium, culture temperature and culture duration. Recommended methods and cultivation conditions can be found in ISO 23500-3, ISO 23500-4 and ISO 23500-5. Low-nutrient media such as R2A agar can be beneficial for isolating slow growing "oligotrophic" bacteria. Classical methodologies using high nutrient media are typically incubated at 30 °C to 35 °C for 48 h to 72 h. Given the flora found in water systems, an incubation at lower temperatures (e.g. 20 °C to 25 °C) and for longer periods (e.g. 5 d to 7 d) can recover higher microbial counts. The culture results obtained using the methods outlined in this document are only a relative indicator of the bioburden and are not a measure of the absolute microbial burden. Furthermore, the advantages gained by incubating for longer times, namely recovery of injured microorganisms, slow growers or more fastidious microorganisms, should be balanced against the need to have a timely investigation and to take corrective action.

The microbial flora of a new water system gradually establishes a steady state relative to the routine maintenance and sanitization procedures over time and is influenced by changes in routine, preventative maintenance or sanitization procedures, or any type of system intrusion, such as for component replacement, removal or addition. Repeated sampling over a period of time enables trends to be established, which form the basis for action levels for the total viable microbial count and endotoxin concentration to be set. Typically, the action levels are set at 50 % of the maximum allowable levels for total viable microbial count and endotoxin, however other levels can be set.

Operators of water treatment systems should also be aware that a low colony count is usually present in the lag phase of bacterial growth, for example shortly after a disinfection, necessitating the samples to be taken before disinfection when the number of bacteria rapidly increases in the exponential phase of bacterial growth, as bacteria had longer time to adapt and proliferate.

D.3.2 Dialysis fluid

The approach in respect of dialysis fluid differs as tests for microbial growth and endotoxins are not required if the dialysis machine fluid pathway is fitted with an appropriate capacity bacteria and endotoxin-retentive filter validated by the manufacturer and operated and surveyed according to the manufacturer's instructions, unless the manufacturer requires such tests in the instructions for use. In case of heavy contamination of the dialysis water, endotoxins and especially short-chain endotoxins, can pass the bacteria and endotoxin retentive filter membrane and under such circumstances a discussion with the medical director is appropriate to decide on the appropriate steps to minimize patient exposure.

If the dialysis machine pathway is not fitted with an bacteria and endotoxin-retentive filter, it is presumed that the treatments are performed with standard dialysis fluid (a total viable microbial count of less than 100 CFU/ml and an endotoxin concentration of less than 0,5 EU/ml). When using such fluid, sampling shall be done from the fluid entering the dialyser coupled with trend analysis. As incubation at lower temperatures (e.g. 20 °C to 25 °C) and for longer periods (e.g. 5 d to 7 d) can recover higher microbial counts than with at an incubation temperature of 35 °C to 37 °C and an incubation time of 48 h, e.g. when using TSA, the decision to use longer incubation times, should balance the need for timely information and the type of corrective actions required when alert or action level is exceeded with the ability of the microorganisms to detrimentally affect the patient due to their exposure to large volumes of dialysis fluid.

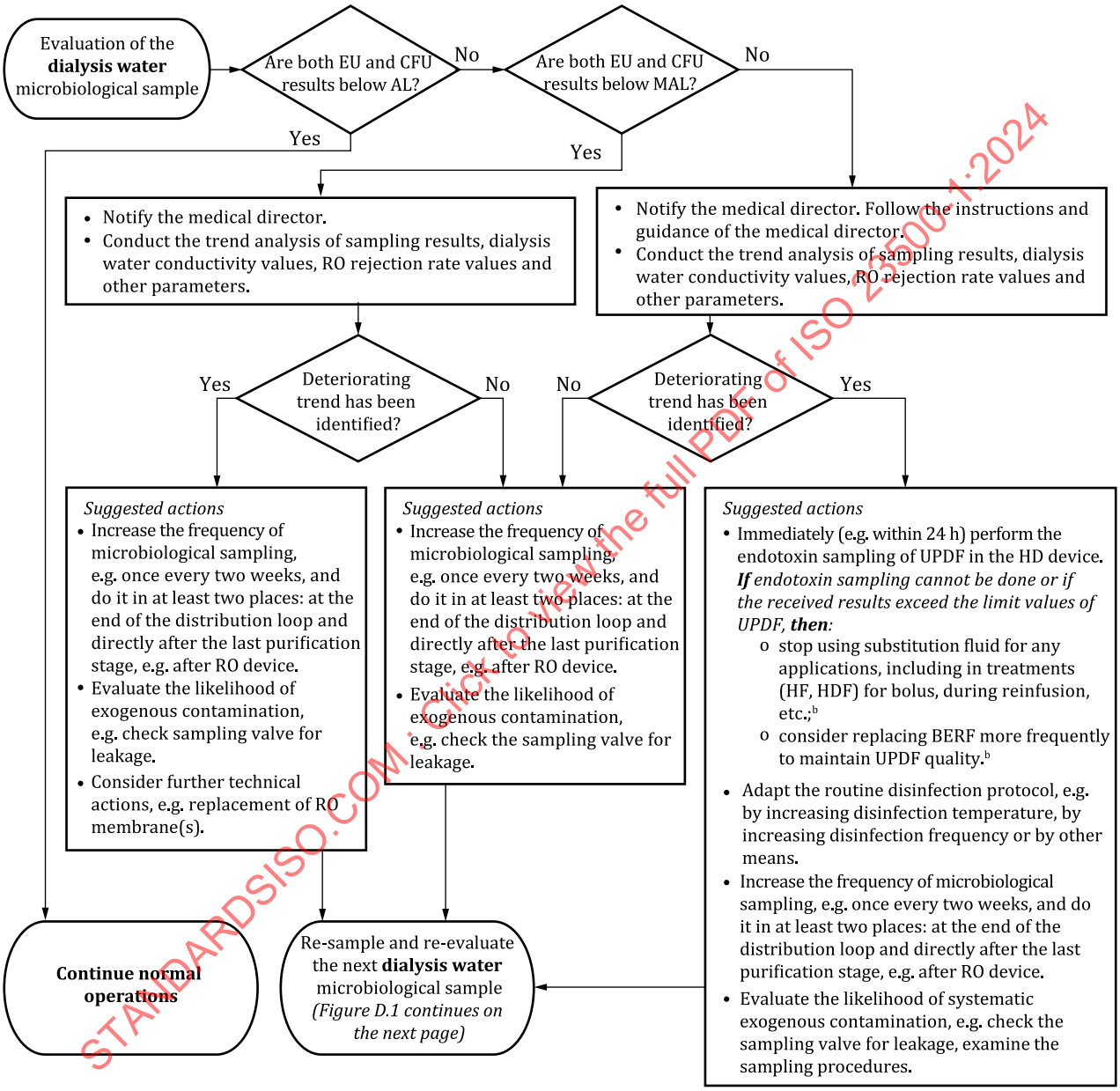
D.3.3 Evaluation of results and corrective actions

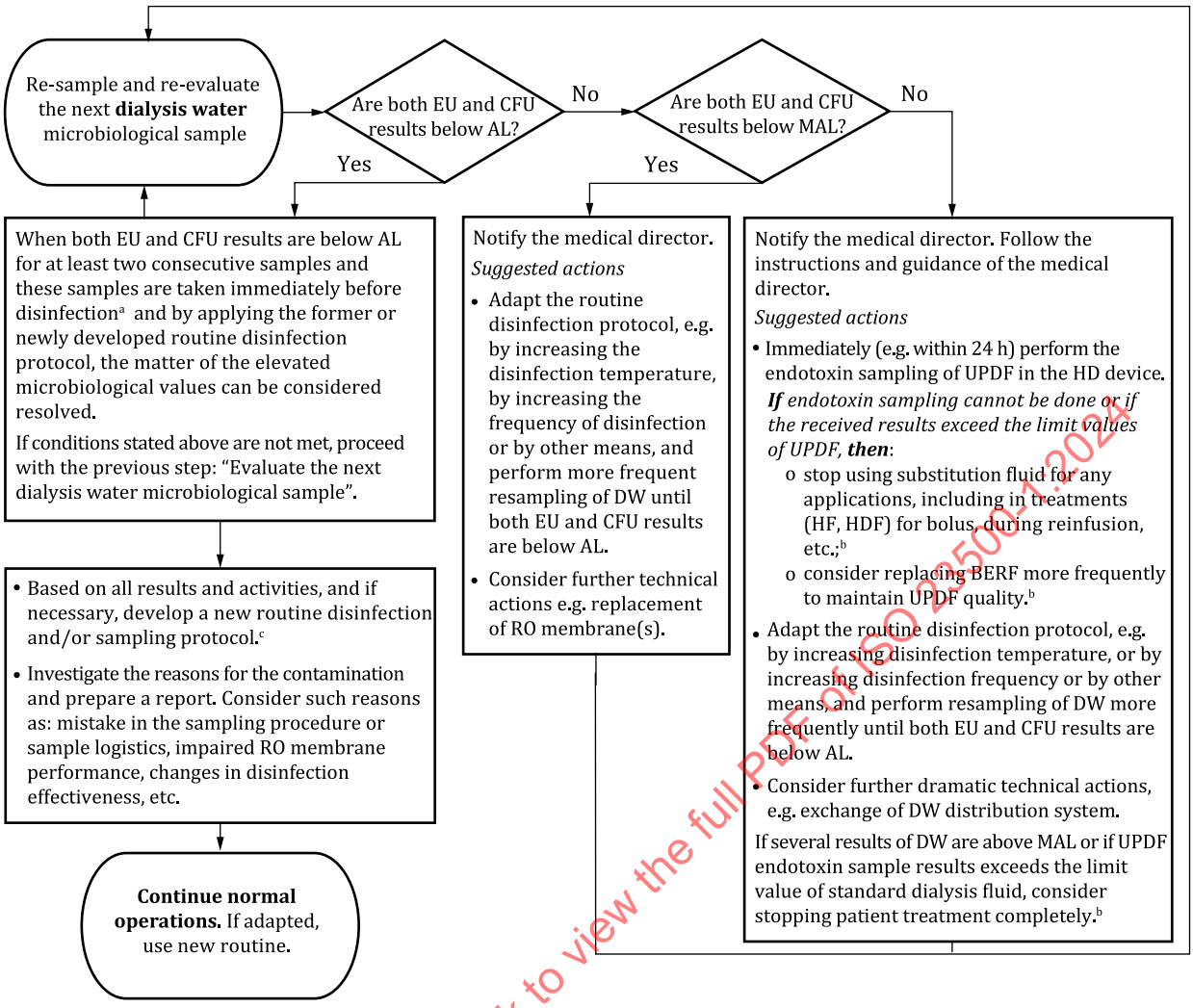
If levels exceeding the action levels are observed in either dialysis water or dialysis fluid, and the levels are below the maximal allowable level (MAL) corrective measures, such as disinfection and retesting, should be performed promptly to reduce the levels and to establish if the observed result is a part of a trend, or an isolated occurrence arising from exogenous sampling-related contamination, there should be awareness

that other reasons for exceeding the limit values are possible such as technical defects, biofilm development and inadequate disinfection.

If the levels exceed both the action levels and the maximum allowable limit, immediate action shall be taken to avoid any risk to the patient and if the dialysis machines are not fitted with a bacterial and endotoxin retentive filter, interruption of treatment should be considered.

Figures D.1 to D.3 are intended to serve as an example of procedures to follow when the action level or the maximal allowable level is exceeded.





Key

AL	action level (typically 50 % of MAL)
BERF	bacteria and endotoxin retentive filter
CFU	colony-forming unit
DW	dialysis water
EU	endotoxin unit
HD	haemodialysis
HDF	haemodiafiltration
HF	Haemofiltration
MAL	maximal allowable level
RO	reverse osmosis
UPDF	ultrapure dialysis fluid (<0,1 CFU/ml; <0,03 EU/ml)

a Limit values (AL and MAL) are typically applicable for samples which are taken just before disinfection, i.e. usually received values represents the "worst-case scenario". For samples taken between disinfections, the impact of time needs to be considered., i.e. how much time has passed from the previous disinfection and how much time till the next disinfection.

b Any changes, restrictions and actions which can influence treatment modality or its parameters shall only be done in agreement with the medical director.

c If protocols have been adapted, revalidation can be necessary.

Figure D.1 — Evaluation of dialysis water microbiological results and suggested corrective actions

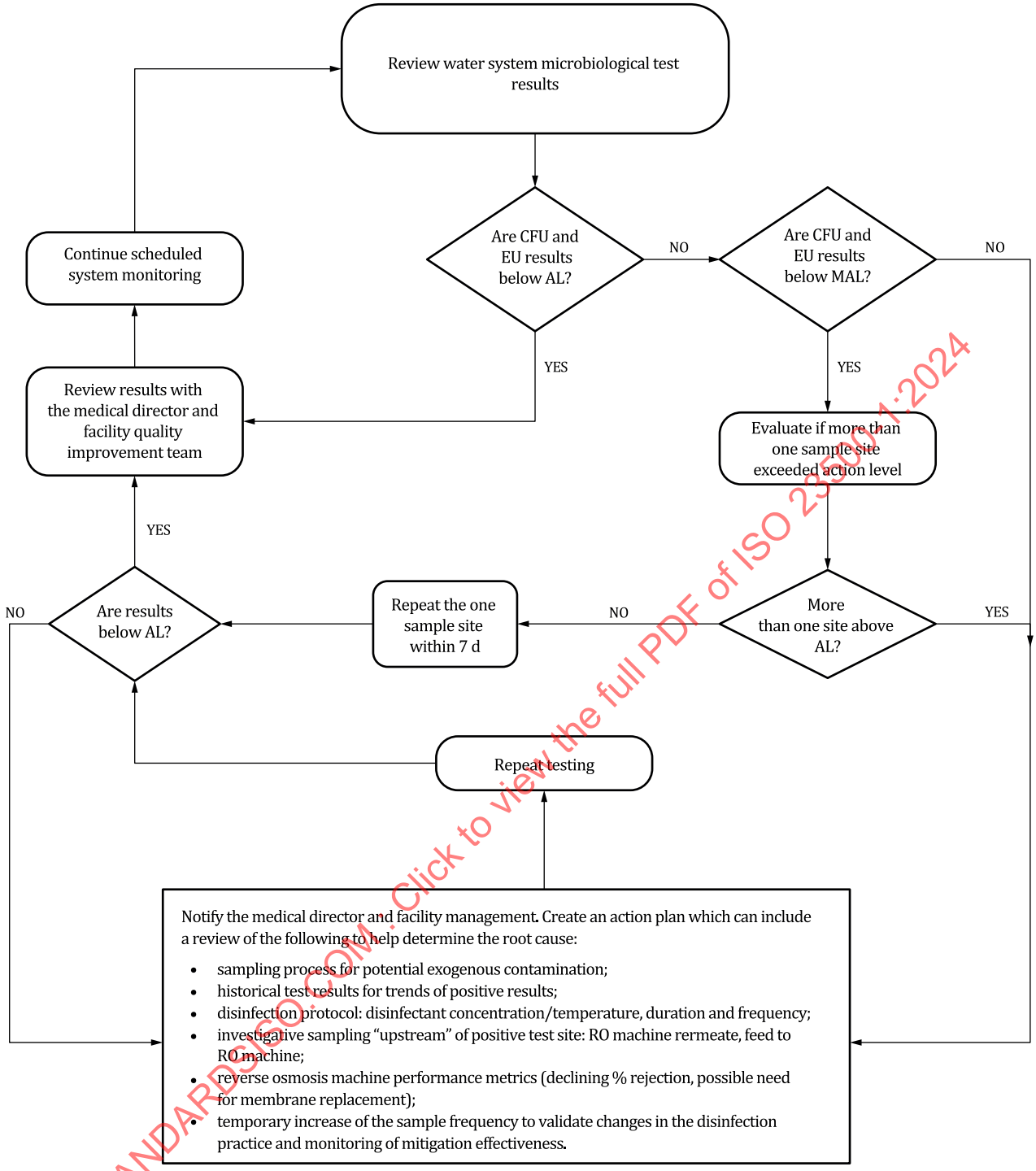


Figure D.2 — Evaluation of dialysis water microbiological results and suggested corrective actions

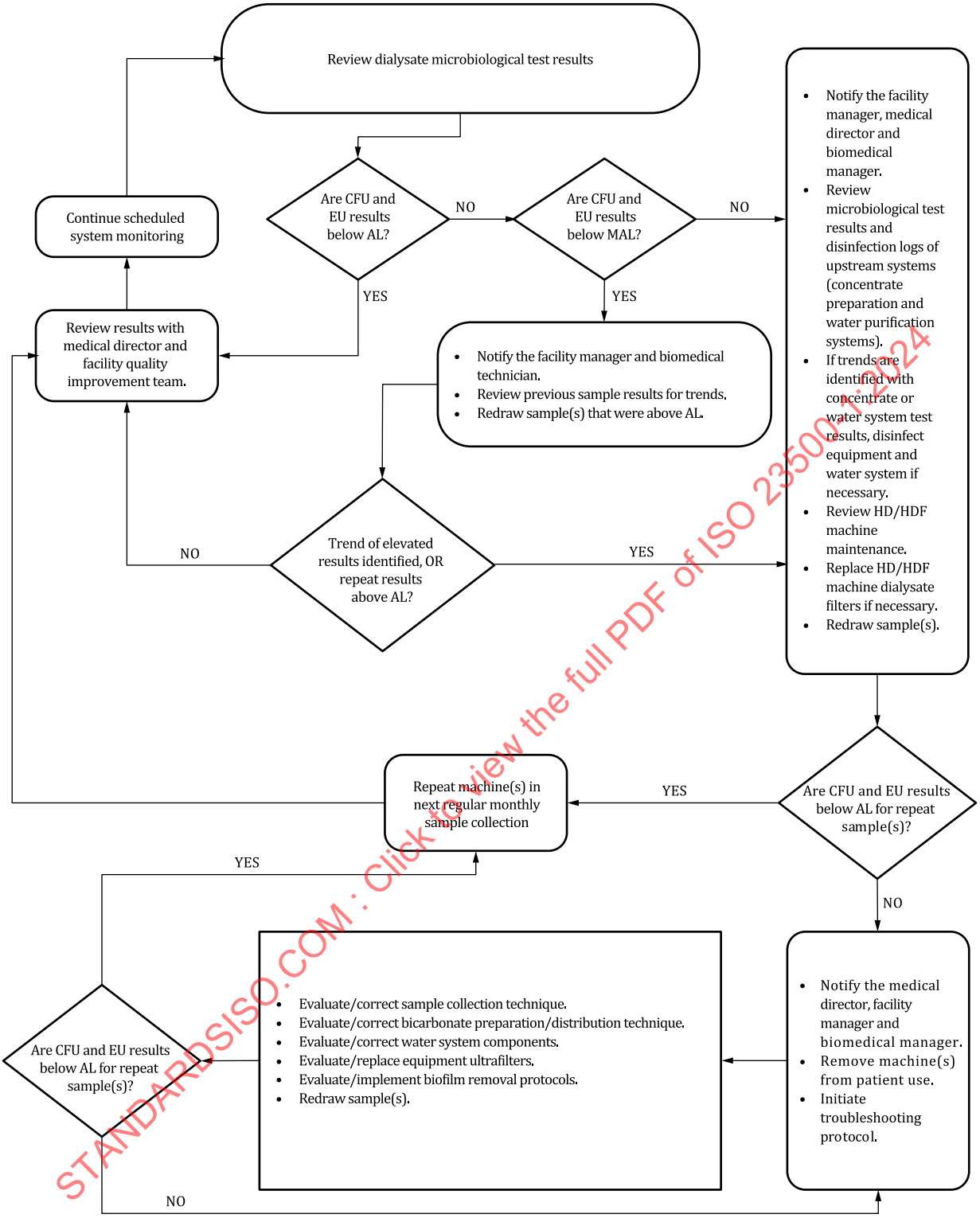


Figure D.3 — Evaluation of dialysis fluid microbiological results and suggested corrective actions

The flowcharts above serves as an example of procedures that may be initiated when action level or maximal allowable level is exceeded. Presumption of the flowchart is that all haemodialysis devices are equipped with bacteria and endotoxin retentive filters and water treatment system have been validated, well maintained and its performance have been stable. Based on experience, if microbiological results of single dialysis water sample are over action level for water treatment system which is validated, well maintained and stable, in great majority of the cases, such values are due to exogenous contamination and not due to contamination

of dialysis water. Other reasons for exceeding the limit values can be due to, for example, technical defects, biofilm development, not adequate disinfection protocol.

Low colony count is usually present in the lag phase of bacterial growth, for example, shortly after a disinfection. Typically, number of bacteria rapidly increases in the exponential phase of bacterial growth, for example, before disinfection, as bacteria had the longest time to adapt and proliferate. When the action level is exceeded, to detect the exponential growth on time, shorter than routine sampling intervals are recommended. For more information, refer to the exponential bacterial growth model.

If the microbiological limit values in dialysis water have been exceeded, a measurement of the endotoxin concentration in ultra-pure dialysis fluid can be used to decide on further treatment related steps. The results of the endotoxin concentration measurements are available much faster than results of colony count, and the risk of exogenous sampling-related contamination is lower than during determination of colony count in ultrapure dialysis fluid. By assuming that bacteria, due to its size, are retained by validated bacteria and endotoxin retentive filters, the main parameters of concern become endotoxins. In case of heavy contamination, endotoxins, and especially short-chain endotoxins, can pass the bacteria and endotoxin retentive filter membrane.

Typically, substitution fluid is prepared by filtration of ultrapure dialysis fluid. Therefore, if the endotoxin concentration in this ultrapure dialysis fluid is shown to meet the required quality level (e.g. <0,03 EU/ml), the use of substitution fluid may be temporarily continued even if the microbiological results of a single dialysis water sample exceed the maximum allowable level (only with the approval of the medical director).

Annex E
(informative)

Validation

E.1 General and background

This annex provides background for Clauses 6 and 8 as well as for Annex C.

The dialysis fluid and the substitution fluid used for online convective therapies are the result of an online process and are used immediately after their production. For this reason, the use of "batch control" techniques based on testing at fixed intervals is not the most effective way to ensure the required quality level is continuously reached. Periodic appraisal of the chemical and microbial fluid quality can miss a potential problem; for example, if that problem arose just after a test sample was collected.

Furthermore, conformity with the requirement that substitution fluid used for online convective therapies be sterile cannot be demonstrated by culturing but is ensured by the application of a validated and adequately monitored process.

The surveillance plan of the overall system (i.e. including the steps from the dialysis water production to the generation of the dialysis fluid and substitution fluid) is based on the knowledge acquired with the validation plan for the specific dialysis water or dialysis fluid production system and the surveillance strategies applicable to the dialysis fluid production devices as validated by the manufacturer.

Moreover, when using a validated and monitored process for removal of bacteria and endotoxins at the dialysis machine, sampling of the substitution fluid is not needed. The presence in the system of parts and equipment (e.g. dialysis machine or endotoxin-retentive filters) that have already been validated by the manufacturer is sufficient to ensure fluid quality, provided those parts and equipment are operated according to the manufacturer's instructions. Sampling of the dialysis water or dialysis fluid should be performed if required by the manufacturer of the validated process.

For these reasons, and under the above-mentioned conditions, an effective surveillance strategy should be based on the direct sampling of the dialysis water and/or dialysis fluid and on surveillance of the process parameters as recommended by the manufacturer and defined by knowledge of the water treatment or dialysis fluid preparation system acquired during the validation phase.

E.2 Validation programme

E.2.1 General

The performance of the dialysis water or dialysis fluid production system should be verified to demonstrate that the system is "fit for purpose". The validation procedure should provide documentary evidence that the process will consistently produce dialysis water, dialysis fluid or substitution fluid meeting the quality requirements of ISO 23500-3 and/or ISO 23500-5.

E.2.2 Validation steps

As described in Clause 6, validation consists of the following:

— validation plan;

— installation and operational qualification;

— performance qualification;

— revalidation through the data collected during routine surveillance.

E.2.3 Validation plan

The validation plan is the road map for successful validation and provides a complete picture of the dialysis facility's validation activities.

The validation plan defines and lists all necessary activities and documentation for

— installation and operational qualification,

— performance qualification, and

— revalidation.

The level of detail in the plan should reflect the risk, complexity and novelty of the system. The validation plan should define all responsibilities during validation and subsequent system operation.

E.2.4 Performance qualification

E.2.4.1 General

As described in Clause 6, the aim of the PQ activity is to establish that the system, as a whole, functions consistently to produce water and dialysis fluid of the required quality when operated according to the defined procedure and with the stipulated raw water characteristics / site conditions.

The prerequisites for the PQ are.

— The demonstration that the plant has been installed according to the design plans and following the installation guideline (i.e. IQ).

— The demonstration that the system performs all the required actions and can be operated according to the user's manual and technical manuals (i.e. OQ).

The PQ includes the periodic assessment of a set of physical, chemical and microbiological parameters to demonstrate that a consistent performance pattern can be achieved.

The PQ strategy has to be adapted to the specific system design and required performance. This sampling and testing pattern can be relaxed during the surveillance phase (normal operation/monitoring) in case the system can demonstrate – over a long time – consistently high-quality results.

NOTE Experience suggests the adoption of a monthly frequency for thermal disinfection of reverse osmosis membranes and chemical disinfection of non-heat disinfectable reverse osmosis systems, including distribution loop, and monthly dialysis water sample collection. For heat disinfectable reverse osmosis systems, a more frequent heat disinfection of distribution loops (including dialysis machines once per week, where applicable) is strongly recommended. This pattern of disinfection ensures an adequate compromise between the running costs and the risks as well as a limitation of the effort required for the retrospective annual validation activity.

Under these assumptions, the PQ can be implemented in two phases.

E.2.4.2 First phase performance qualification

During this period, all the information about the system behaviour should be collected and the fine-tuning of the action levels should be performed. In this phase, the testing frequency of the microbiological parameters is kept at a higher level to create a 'trend analysis' and identify any deviations to ensure the patients safety. The goal is to demonstrate the consistent quality in the interval between the defined disinfection intervals. Longer intervals can require additional microbiological sampling in the first phase performance qualification (PQ-1) phase to ensure truly continuous coverage throughout this period.

The first chemical and microbiological analysis is performed at the start of PQ-1.

The patients' treatment can be initiated after the availability of the first results of the chemical and microbiological analyses showing that the dialysis water is compliant with the required quality. The medical director of the renal unit or their designated deputy should approve the release for patient treatments in written form. The designated deputy should be a person who is informed about the validation steps and/or is responsible for operational aspects of the water treatment.

The first phase PQ-1 should cover the period of the planned routine sampling or disinfection interval. The longer of the two should be defined as this interval, i.e. either the sampling or the disinfection interval. During this period, microbiological sampling should be performed repeatedly and results of at least three consecutive samples should be below the action level to start the second phase PQ-2. In case of a negative trend (increasing values) or values above the action level, the disinfection and/or microbiological surveillance interval should be shortened.

The following sampling should be performed preferably prior to disinfection or, alternatively, not sooner than 24 h after the disinfection process, to avoid false negative results and to demonstrate the adequate system behaviour. The samples taken after the disinfection are used to demonstrate the effectiveness of the disinfecting procedure; they should be taken after the first monthly disinfection (after start-up of the water treatment system) and in case of troubleshooting.

The following minimum sampling plan is suggested for the first phase of the PQ-1:

— chemical analyses on:
  — raw water (if not available from the supplier);
  — pre-treated (RO inlet) water;
  — dialysis water;
— microbiological analyses (samples to be taken not sooner than 24 h after the first water treatment and distribution system disinfection) on dialysis water;
— when adequate results are achieved the patients' treatment can be initiated (typically at least one week after the PQ start date due to the 7 d required to complete the incubation period for the microbiological analysis);
— microbiological analyses in intervals according to the validation plan (see Table E.1) on dialysis water.

E.2.4.3 Second phase performance qualification

In the second phase of the PQ, two consecutive microbiological samples at the designated sampling and disinfection intervals should be below the action level. This allows the successful completion of the PQ and the start of the routine surveillance operations.

During second phase performance qualification (PQ-2), the following minimum sampling plan is suggested for the period as defined in the validation plan: microbiological analysis in intervals according to the validation plan (samples to be taken preferably prior to disinfection or, alternatively, not sooner than 24 h after the disinfection process, to avoid false negative results) on dialysis water.

E.2.5 Routine surveillance

The successful completion of the PQ allows the starting of the routine surveillance phase that implies:

— microbiological analysis in intervals according to validation results (samples to be taken preferably prior to disinfection or, alternatively, not sooner than 24 h after the disinfection process, to avoid false negative results) on dialysis water;
— yearly full chemical analysis on:
  — raw water (if not available from the supplier),
  — pre-treated (RO inlet) water,

— dialysis water;

— routine system disinfection as established in the PQ;

— annual retrospective or continuous validation upon the successful completion of the tests.

Each analysis and test can be also triggered by any significant deviation in the process parameters (e.g. conductivity) suggesting possible system malfunctions or changes in the raw water characteristics.

Table E.1 — PQ activities: Example of disinfection and routine surveillance intervals scheme

Disinfection type of RO system	RO type	Disinfection interval	Routine surveillance	Recommendation level	PQ-1 and sampling interval of *x* weeks after previous sampling (0 = after start-up)	PQ-2 and routine sampling interval
Thermal	Large RO	Weekly	M	Highest	0-2-2	M-M
			Q	Medium	0-2-5-6	Q-Q
			S	Minimum	0-2-5-8-12 or 0-2-8-16	S-S
Chemical	Large RO	M[b]	M	Highest	0-1-1-1(-1)[a]	M-M
			Q	Medium	0-2-2-4-5	Q-Q
		Q[b]	M	Medium	0-2-2-4-5	M-M
			Q	Minimum	0-2-2-4-5	Q-Q

Key

M monthly

Q quarterly

S semi-annual

[a] Weekly intervals until first monthly routine disinfection (sampling before disinfection).

[b] Disinfection interval can be adapted depending on the validation results.

It is recommended to follow the "highest" approach of PQ. Once continuous WTS operation below action levels and no negative trend can be demonstrated (e.g. during routine revalidation activities), it can be considered to relax the disinfection/sampling intervals according to the table, if required.

If the disinfection interval is intended to be extended in a validated and stable system, a revalidation (new validation) from phase PQ-1 should be performed (sampling immediately before the last disinfection corresponds to the first sample of PQ-1).

If the microbiological sampling interval is intended to be extended in a validated and stable water treatment (WT) system (values below AL), a revalidation from PQ-2 should be performed. To support the decision to extend the sampling interval in a safe way, it should be demonstrated that the retrospective microbiological analyses results have been consistently below action level for a minimum duration of the last PQ (PQ-1 and at least the first sample of PQ-2) phase.

A microbiological sampling interval of three months should not be exceeded and it is strongly advised against for large ROs with chemical disinfection.

An exception is made for systems with consistently good hygiene management (e.g. weekly heat disinfection, regular rinsing cycles, operation according to manufacturer's instructions); an interval of maximum six months can be considered.

E.3 Consequences for the surveillance strategy

As a result of the validation process for the water treatment or dialysis fluid preparation system, adequate maintenance and routine surveillance plans are established. Based on these regimes, system surveillance starts after performance qualification and ensures ongoing conformance to quality criteria regarding dialysis fluid and in-house produced concentrates.

Trend analysis through surveillance should be used as a source of advanced information on system performance, thus enabling a proactive approach to system maintenance with consequential operational and financial benefits.

Surveillance is achieved with online and offline measurements. With current technology, the majority of parameters are measured offline. Table C.1 lists possible surveillance parameters and related frequencies of measurement.

The online surveillance of suitable parameters (such as conductivity) provides immediate identification of deviations from normal operating conditions, offering the following advantages:

— timely identification of potential problems in their early stage;

— quick and easy diagnosis of the root causes (incoming water quality/technical malfunction);

— implementation of necessary countermeasures;

— triggering of specific offline measurements.

As mentioned earlier, a purely time-based offline sampling regime has inherent limitations for the surveillance of a continuous production process since deviations can occur during the sampling intervals.

E.4 Guidance on technical needs after typical technical interventions

Guidance on the different technical needs (e.g. disinfection, extraordinary analysis, re-validation) after typical technical interventions is given in this clause.

Table E.2 can be used as a decision matrix for procedures to be performed in case of technical intervention in the water treatment system or concentrates distribution system.

The following scheme is applicable for single-stage and double-stage RO devices, unless otherwise defined.

— Up-to-date manufacturer's instructions should always be followed.

— Only original components/spare-parts should be used.

— Chemical composition of raw water must be compliant with WHO.

— For newly implemented water treatment systems, the supply of dialysis fluids for patients' treatments can be initiated by the medical director of the clinic upon the availability of the first test results of chemical and microbial analysis that are fully in compliance with all limit values that are defined in this document or manufacturer’s specifications.

— If only parts of the WTS have been replaced, the release on concession under specific requirements can be given before final results of the laboratory analyses are available (concurrent validation supported by risk assessment, see Annex I).

— "recommended", i.e. depending on repairs; for example, when minor repairs are performed (e.g. small parts in contact with dialysis water), sampling is not always necessary; if major repairs (e.g. large material surfaces in contact with dialysis water) have been performed, microbiological sampling should be carried out.

Table E.2 — Procedures to be undertaken after technical interventions in the water treatment system and concentrates distribution system

Technical intervention	Procedure							
	Disinfection (depending on RO device, select thermal or chemical disinfection mode)	Chemical disinfection (ring main and RO membrane)	Thermal disinfection of loop main	Thermal disinfection of RO membrane[b]	Revalidation	Further tests (e.g. pressure, volume, physical parameters)	Microbiological test	Chemical test
Repair on the pre-treatment, routine exchange of media	No	No	No	No	No	See manufacturer's instructions	No	No[f]
Replacement or optimisation of pre-treatment[e]	No	No	No	No	No[d]	See manufacturer's instructions	No	Yes[g]
Replacement of complete pre-treatment or individual components (identical media/materials)	No	No	No	No	No	See manufacturer's instructions	No	No[a]
Repair on the RO concentrate side	No	No	No	No	No	See manufacturer's instructions	No	No

Key

NA not applicable

a For example, the replacement of old pre-treatment with new one.

b Thermal disinfectable membranes can require thermal conditioning after installation (see manufacturer's instructions).

c Disinfection and sampling plans should be revised and adapted according to analyses results.

d "Reduced revalidation", focusing on affected chemical parameter(s), contains IQ, OQ and chemical measurement of affected parameters as per PQ; microbiological sampling of dialysis water not required.

e For example, the size of the active carbon has been changed or doubled, triggered by, for example, corrective action; installation of additional filters, e.g. nitrate.

f All feed water parameters must be compliant with local drinking water regulation or WHO; quality of the pre-treated water must be compliant with requirements for RO supply.

g Provides evidence for the efficacy of, for example:

— corrective action;

— regular monitoring of chemical parameters in pre-treated water (and in dialysis water if applicable) that led to the need of replacement/optimisation of pre-filtration (e.g. to increase AC filter size, nitrates);

— compliance with WHO for all chemical feed water parameters (note that local drinking water regulations can apply);

— compatibility of pre-treatment for RO operation (e.g. capacity/soft water delivery volume);

— use of quick analysis kits, e.g. for nitrate, is recommended to provide fast evidence of corrective action/successful optimisation of water treatment system; quality of the pre-treated water must be compliant with requirements for reverse osmosis supply;

— full chemical analysis of feed water (e.g. by water supplier) that has been analyzed before the replacement of pre-treatment[a] (changes of feed water quality composition have been checked by own sampling or water supplier analysis);

— regular monitoring of chemical parameters in pre-treated water which led to the need of replacement/optimisation of pre-filtration.

h One-time sampling, not sooner than 24 h after disinfection.

i Full chemical analysis.

j Not required, since extension of distribution loop will Not influence chemical performance of RO and/or chemical composition of the dialysis water.

Table E.2 *(continued)*

Technical intervention	Procedure							
	Disinfection (depending on RO device, select thermal or chemical disinfection mode)	**Chemical disinfection (ring main and RO membrane)**	**Thermal disinfection of loop main**	**Thermal disinfection of RO membrane[b]**	**Revalidation**	**Further tests (e.g. pressure, volume, physical parameters)**	**Microbiological test**	**Chemical test**
Repair on the RO dialysis water side	Either chemical or thermal	Yes	No, if only RO affected Yes, if only loop affected	Yes, if only RO affected No, if only loop affected	No	See manufacturer's instructions	— if single stage RO: yes (recommended)[d] — if double stage RO (repair before 2nd stage): no — if double stage RO (repair after 2nd stage): yes (recommended) — if ultrafilter after RO is installed: no	No
RO membrane replacement (unmodified specification)	Either chemical or thermal	Yes	No	Yes	No	See manufacturer's instructions	Yes[c h]	No
RO module modification or upgrade	Either chemical or thermal	Yes	No	Yes	Yes	See manufacturer's instructions	Yes[c] (see validation)	Yes[i]
Complete RO replacement	Either chemical or thermal	Yes	Yes	Yes	Yes	See manufacturer's instructions	Yes[c] (see validation)	Yes[i]

Key

NA not applicable

a For example, the replacement of old pre-treatment with new one.

b Thermal disinfectable membranes can require thermal conditioning after installation (see manufacturer's instructions).

c Disinfection and sampling plans should be revised and adapted according to analyses results.

d "Reduced revalidation", focusing on affected chemical parameter(s), contains IQ, OQ and chemical measurement of affected parameters as per PQ; microbiological sampling of dialysis water not required.

e For example, the size of the active carbon has been changed or doubled, triggered by, for example, corrective action; installation of additional filters, e.g. nitrate.

f All feed water parameters must be compliant with local drinking water regulation or WHO; quality of the pre-treated water must be compliant with requirements for RO supply.

g Provides evidence for the efficacy of, for example:

— corrective action;

— regular monitoring of chemical parameters in pre-treated water (and in dialysis water if applicable) that led to the need of replacement/optimisation of pre-filtration (e.g. to increase AC filter size, nitrates);

— compliance with WHO for all chemical feed water parameters (note that local drinking water regulations can apply);

— compatibility of pre-treatment for RO operation (e.g. capacity/soft water delivery volume);

— use of quick analysis kits, e.g. for nitrate, is recommended to provide fast evidence of corrective action/successful optimisation of water treatment system; quality of the pre-treated water must be compliant with requirements for reverse osmosis supply;

— full chemical analysis of feed water (e.g. by water supplier) that has been analyzed before the replacement of pre-treatment[a] (changes of feed water quality composition have been checked by own sampling or water supplier analysis);

— regular monitoring of chemical parameters in pre-treated water which led to the need of replacement/optimisation of pre-filtration.

h One-time sampling, not sooner than 24 h after disinfection.

i Full chemical analysis.

j Not required, since extension of distribution loop will Not influence chemical performance of RO and/or chemical composition of the dialysis water.

Table E.2 *(continued)*

Technical intervention	Procedure							
	Disinfection (depending on RO device, select thermal or chemical disinfection mode)	Chemical disinfection (ring main and RO membrane)	Thermal disinfection of loop main	Thermal disinfection of RO membrane[b]	Revalidation	Further tests (e.g. pressure, volume, physical parameters)	Microbiological test	Chemical test
Repair on the dialysis water ring/media supply	Either chemical or thermal	Yes	Yes	No	No	See manufacturer's instructions	Yes[c h]	No
Extension/additional distribution loop	Either chemical or thermal	Yes	Yes	No	Yes	See manufacturer's instructions	Yes[c]	No[j]
Acid concentrate distribution system	NA	NA	NA	NA	No	See manufacturer's instructions	No	No

Key

NA not applicable

a For example, the replacement of old pre-treatment with new one.

b Thermal disinfectable membranes can require thermal conditioning after installation (see manufacturer's instructions).

c Disinfection and sampling plans should be revised and adapted according to analyses results.

d "Reduced revalidation", focusing on affected chemical parameter(s), contains IQ, OQ and chemical measurement of affected parameters as per PQ; microbiological sampling of dialysis water not required.

e For example, the size of the active carbon has been changed or doubled, triggered by, for example, corrective action; installation of additional filters, e.g. nitrate.

f All feed water parameters must be compliant with local drinking water regulation or WHO; quality of the pre-treated water must be compliant with requirements for RO supply.

g Provides evidence for the efficacy of, for example:

— corrective action;

— regular monitoring of chemical parameters in pre-treated water (and in dialysis water if applicable) that led to the need of replacement/optimisation of pre-filtration (e.g. to increase AC filter size, nitrates);

— compliance with WHO for all chemical feed water parameters (note that local drinking water regulations can apply);

— compatibility of pre-treatment for RO operation (e.g. capacity/soft water delivery volume);

— use of quick analysis kits, e.g. for nitrate, is recommended to provide fast evidence of corrective action/successful optimisation of water treatment system; quality of the pre-treated water must be compliant with requirements for reverse osmosis supply;

— full chemical analysis of feed water (e.g. by water supplier) that has been analyzed before the replacement of pre-treatment[a] (changes of feed water quality composition have been checked by own sampling or water supplier analysis);

— regular monitoring of chemical parameters in pre-treated water which led to the need of replacement/optimisation of pre-filtration.

h One-time sampling, not sooner than 24 h after disinfection.

i Full chemical analysis.

j Not required, since extension of distribution loop will Not influence chemical performance of RO and/or chemical composition of the dialysis water.

Annex F
(informative)

Special considerations for home haemodialysis

F.1 General

The quality of dialysis water used to prepare concentrate and dialysis fluid is as important for home haemodialysis as it is for in-centre haemodialysis. This document is written principally to address equipment used for in-centre haemodialysis. While many of the provisions of this document are also applicable to home haemodialysis, the latter treatment may pose some special challenges not encountered with in-centre haemodialysis. Similarly, home haemodialysis can require some departures from the provisions of this guidance regarding dialysis fluid preparation. Given the renewed interest in home haemodialysis and, in particular, the use of more frequent treatment schedules, this annex has been included to address some of the concerns particular to the home haemodialysis setting. The recommendations included in this annex apply to water treatment systems assembled from individual components. Some of the recommendations in this annex do not always apply to systems for home haemodialysis containing integrated water treatment equipment designed and validated to produce water and dialysis fluid of the quality required by ISO 23500-3 and ISO 23500-5. Validated systems require assurance that the system is being operated under the validated conditions. Also, the recommendations of this annex do not apply to sorbent-based dialysate regeneration systems, which are excluded from the scope of this document.

Home haemodialysis differs from in-centre haemodialysis in that the patient or a helper will be responsible for day-to-day operation and maintenance of the water treatment and other dialysis equipment. In general, these individuals do not have formal technical training in haemodialysis. Therefore, the dialysis centre should provide training in the operation and maintenance of the equipment and require a demonstration of competence in those areas before home treatments are begun.

F.2 Fluid quality

Dialysis water, concentrate and dialysis fluid used for home haemodialysis applications should meet the quality requirements set forth in ISO 23500-3, ISO 23500-4:2024, Clause 4 and ISO 23500-5:2024, Clause 4.

F.3 Utilities

F.3.1 General

To incorporate a haemodialysis machine in a home, the home will need a water supply, a drain connection and a dedicated power source. It is recommended that the utility companies providing water and power to the patient's home be notified that home dialysis is being performed at that location and that restoring service following any interruption should be considered a priority.

F.3.2 Water supply

If the water is supplied by a municipal water system, it should meet the applicable standards for drinking water. Periodic appraisal of the water supply should be performed to confirm that it meets the requirements of this document.

If the water is not supplied by a municipal water system but obtained from a private well, applicable drinking water standards can differ depending on the number of households that the well supplies. Furthermore, regulatory requirements with different indications can apply with respect to surveillance. In view of this, the water supply should be analysed more frequently than in a hospital-based dialysis unit, especially if the location is rural. The water source in such situations can be subject to seasonal changes, such as heavy rain