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

Part 2: Water treatment equipment for haemodialysis applications and related therapies

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

Partie 2: Équipement de traitement de l'eau pour des applications en hémodialyse et aux thérapies apparentées

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

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

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

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

For an explanation of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT) see www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 150, *Implants for surgery*, Subcommittee SC 2, *Cardiovascular implants and extracorporeal systems*.

This first edition cancels and replaces ISO 26722:2014, which has been technically revised. The main changes compared to the previous edition are as follows:

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

A list of all parts in the ISO 23500 series can be found on the ISO website.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

This document reflects the conscientious efforts of concerned physicians, clinical engineers, nurses, dialysis technicians, and dialysis patients, in consultation with device manufacturers and regulatory authority representatives, to develop an International Standard for performance levels that could be reasonably achieved at the time of publication. The term “consensus,” as applied to the development of voluntary medical device documents, does not imply unanimity of opinion, but rather reflects the compromise necessary in some instances when a variety of interests should be merged.

This document applies to individual water treatment devices and to water treatment systems assembled from one or more of these devices. In the first instance, this document is directed at the individual or company that specifies the complete water treatment system and, second, at the supplier who assembles and installs the system. Since systems can be assembled from a number of individual water treatment devices, the provisions of this document are also directed at the manufacturers of these devices, provided that the manufacturer indicates that the device is intended for use in haemodialysis applications. This document is written principally to address water treatment systems for dialysis facilities treating multiple patients. However, many of its provisions apply equally to water treatment systems used in applications where a single patient is treated, such as in a home dialysis or acute hospital dialysis setting. Specifically, requirements for the chemical and microbiological quality of water are considered to apply in all settings, regardless of whether a single patient or many patients are being treated.

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

This document helps protect haemodialysis patients from adverse effects arising from known chemical and microbial contaminants found in water supplies. However, dialysis and patient safety is ultimately dependent on the quality of the dialysis fluid. Since the manufacturer or supplier of water treatment equipment does not have control over the dialysis fluid, any reference to dialysis fluid in this document is for clarification only and not a requirement of the manufacturer. The responsibility for assuring that the dialysis fluid is not contaminated, mismatched, or otherwise damaging to the patient rests with the clinical professionals caring for the patient under the supervision of the medical director. Requirements and recommendations on the preparation and handling of water and dialysis fluid in a dialysis facility are provided in ISO 23500-5. The rationale for the development of this document is given in Annex A.

Since the chemical and microbiological content of the water produced need to meet the requirements of ISO 23500-3, the maximum allowable levels of contaminants are listed in Annex B (Tables B.1 and B.2). The values shown include the anticipated uncertainty associated with the analytical methodologies listed in Table B.3.

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

Part 2:
Water treatment equipment for haemodialysis applications and related therapies

1 Scope

1.1 General

This document is addressed to the manufacturer and/or supplier of water treatment systems and/or devices used for the express purpose of providing water for haemodialysis or related therapies.

1.2 Inclusions

This document covers devices used to treat potable water intended for use in the delivery of haemodialysis and related therapies, including water used for:

a) the preparation of concentrates from powder or other highly concentrated media at a dialysis facility;

b) the preparation of dialysis fluid, including dialysis fluid that can be used for the preparation of substitution fluid;

c) the reprocessing of dialysers intended for single use where permitted for multiple uses,

d) the reprocessing of dialysers not specifically marked as intended for single use.

This document includes all devices, piping and fittings between the point at which potable water is delivered to the water treatment system, and the point of use of the dialysis water. Examples of the devices are water purification devices, online water quality monitors (such as conductivity monitors), and piping systems for the distribution of dialysis water.

1.3 Exclusions

This document excludes dialysis fluid supply systems that proportion water and concentrates to produce dialysis fluid, sorbent dialysis fluid regeneration systems that regenerate and recirculate small volumes of the dialysis fluid, dialysis concentrates, haemodiafiltration systems, haemofiltration systems, systems that process dialysers for multiple uses, and peritoneal dialysis systems. Some of these devices, such as dialysis fluid delivery systems and concentrates, are addressed in other documents such as ISO 23500-4 and ISO 23500-5,

This document also excludes the on-going surveillance of the purity of water used for dialysis fluid, concentrate preparation, or dialyser reprocessing which is addressed in ISO 23500-1.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 23500-1:2019, *Preparation and quality management of fluids for haemodialysis and related therapies — Part 1: General requirements*

ISO 23500-3:2019, *Preparation and quality management of fluids for haemodialysis and related therapies — Part 3: Water for haemodialysis and related therapies*

IEC 60601-1-8, *Medical electrical equipment — Part 1-8: General requirements for basic safety and essential performance — Collateral standard: General requirements, tests and guidance for alarm systems in medical electrical equipment and medical electrical systems*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 23500-1 and the following apply.

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

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

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

3.1
microfilter
filter designed to remove particles down to 0,1 µm in size

Note 1 to entry: Microfilters have an absolute size cut-off and are available in both dead-end and cross-flow configurations. Some microfilters can reduce the concentration of endotoxins by adsorption.

4 Requirements

4.1 Dialysis water quality requirements

4.1.1 General

The requirements contained in this document apply to the dialysis water as it enters the equipment used to prepare concentrates from powder or other concentrated media at a dialysis facility, to prepare dialysis fluid, or to reprocess dialysers. As such, these requirements apply to the water treatment system as a whole and not to each of the individual devices that make up the system. However, collectively, the individual devices shall produce dialysis water that, at a minimum, meets the requirements of the clause.

4.1.2 Chemical contaminant requirements

Dialysis water used to prepare dialysis fluid or concentrates from powder at a dialysis facility, or to reprocess dialysers for multiple uses, shall not contain chemical contaminants at concentrations in excess of those in ISO 23500-3:2019, Tables 1 and 2 (reproduced as Tables B.1 and B.2). The manufacturer or supplier of a complete water treatment system shall recommend a system capable of meeting the requirements of this clause based on the analysis of the feed water. The system design should reflect possible seasonal variations in feed water quality. The manufacturer or supplier of a complete water treatment and distribution system shall demonstrate that the complete water treatment, storage, and distribution system is capable of meeting the requirements of this document at the time of installation.

NOTE 1 If the manufacturer or supplier does not install the water storage and distribution system, then the responsibility of the manufacturer or supplier is limited to demonstrating that the water treatment system, excluding the water storage and distribution system, meets the requirements of this document. If individual devices of the water treatment system are provided by different manufacturers or suppliers, the person or organization specifying the devices is responsible for demonstrating that the complete system meets the requirements of this document at the time of installation.

For disposable water treatment and distribution systems that have been validated to produce dialysis water meeting the quality requirements of this document for a specified time, surveillance of the

incoming potable water is required to ensure that the input to the treatment system is in the range for which the system has been validated. The manufacturer's recommendation for surveilling the final dialysis water can be followed when the system is operated according to the manufacturer's instructions. Alternatively, the quality of the dialysis water can be closely observed as outlined for non-validated systems.

NOTE 2 Following the installation of a water treatment, storage, and distribution system, the user is responsible for continued surveillance of the levels of chemical contaminants in the water and for complying with the requirements of this document.

4.1.3 Organic Carbon, pesticides and other chemicals

The presence of organic compounds, such as pesticides, polycyclic aromatic hydrocarbons and other chemicals such as pharmaceutical products and endocrine disruptors in respect of hemodialysis patients are difficult to define. Consequences of exposure are probably of a long-term nature and it is technically difficult and costly to measure these substances on a routine basis. Furthermore, there is an absence of evidence of their widespread presence in water although it is recognized that inadvertent discharges are possible. In view of this, it is not possible to currently define limits for their presence in water used in the preparation of dialysis fluid.

Nanofiltration and reverse osmosis are capable of significant rejection of many such compounds. Granular Activated Carbon (GAC) is also highly effective at removing majority of such compounds. However, as Granular Activated Carbon is widely used in the removal of chlorine/chloramine, their use in the removal of organic carbons, pesticides and other chemicals will be dependent upon the size of the carbon filters and/or beds and users shall be aware of appropriate dimensioning since the majority of carbon valences might be already occupied and not available for further removal activity.

4.1.4 Microbiology of dialysis water

Dialysis water used to prepare dialysis fluid or concentrates from powder at a dialysis facility, or to reprocess dialysers for multiple uses, shall contain a total viable microbial count and endotoxin levels as specified in ISO 23500-3.

The manufacturer or supplier of a complete water treatment and distribution system shall demonstrate that the complete water treatment, storage, and distribution system meets the requirements of this document, including those related to action levels at the time of installation.

NOTE 1 If the manufacturer or supplier does not install the water storage and distribution system, then the responsibility of the manufacturer or supplier is limited to demonstrating that the water treatment system, excluding the water storage and distribution system, meets the requirements of this document. If individual devices of the water treatment system are provided by different manufacturers or suppliers, the person or organization specifying the devices is responsible for demonstrating that the complete system meets the requirements of this document at the time of installation.

For disposable water treatment systems validated by the manufacturer to produce dialysis water meeting the quality requirements of this document for a specified time, surveillance of the incoming feed water is required to ensure that the input to the treatment system is in the range for which the system has been validated. The manufacturer's recommendations for surveilling the dialysis water can be followed when the system is operated according to the manufacturer's instructions. Alternatively, the quality of the dialysis water can be observed as outlined for non-validated systems.

NOTE 2 Following installation of a water treatment, storage, and distribution system, the user is responsible for continued surveillance of the water bacteriology of the system and for complying with the requirements of this document, including those requirements related to action levels.

4.2 Water treatment equipment requirements

4.2.1 General

4.2.1.1 Water treatment system

The supplier of the feed water or the supplier of the water treatment system or a laboratory specified by the user shall perform chemical analyses on feed water to determine the compatibility of the system with the feed water and the suitability of the system for providing dialysis water meeting the requirements of 4.1.2. The result of the chemical analyses shall be available to the user in charge of dialysis. In the case of an individual device, the person incorporating the device into the water treatment system is responsible for ensuring that incorporation of the device does not compromise the ability of the overall system to deliver dialysis water capable of meeting the requirements of 4.1.2 and 4.1.4.

The water treatment and distribution system should include appropriate pressure gauges, flow meters, sample ports, and other ancillary equipment necessary to allow surveillance of the performance of individual system devices and the system as a whole.

Valves can be included in the water treatment system to allow individual devices to be bypassed when there is device failure or to facilitate replacement of a device. If it is possible to bypass a device of the water treatment system, then the manufacturer or installer of that component shall inform the user of the risks associated with bypassing that device and the need for clearly defining the responsibility for operating the bypass. Where such valves are installed, however, a means should be included to minimize the likelihood that the device will be inadvertently bypassed during normal operation of the system.

Operating controls shall be positioned so as to minimize inadvertent resetting.

Electrical circuits shall be separate from hydraulic circuits and adequately protected from fluid leaks.

4.2.1.2 Materials compatibility

Materials that are in contact with dialysis water (including materials used in piping, storage, and distribution systems) shall not interact chemically or physically with that water so as to adversely affect its purity or quality. Water-contacting surfaces shall be fabricated from non-reactive materials (e.g. plastics) or appropriate stainless steel. The use of materials known to cause toxicity in haemodialysis, such as copper, brass, galvanized metal, or aluminium, are specifically prohibited at any point beyond the water treatment device used to remove contaminating metal ions, most commonly a reverse osmosis system or a deionizer. The materials of any water treatment devices (including piping, storage, and distribution systems) shall be compatible with the means used to disinfect those devices. Chemicals infused into the water in the pre-treatment section, such as chlorine, acid, flocculants, and complexing agents, shall be adequately removed from dialysis water before they reach any point of use. Monitors or specific test procedures to verify removal of additives shall be provided.

4.2.1.3 Regenerated or reconstituted devices

All devices that are regenerated or reconstituted at a site remote from the dialysis facility, such as deionizers, shall be disinfected at the time of regeneration or reconstitution, so that contaminated water is not reintroduced into the system after regeneration or reconstitution. Separate processes shall be used to ensure no intermixing of devices or their component parts between devices returned from medical or potable water users and devices returned from non-potable water users.

4.2.1.4 Disinfection protection

When the manufacturer recommends chemical disinfectants [see 6.3 x)], means shall be provided to restore the equipment and the system in which it is installed, to a safe condition relative to residual disinfectant prior to the dialysis water being used for dialysis applications. When recommending chemical disinfectants, the manufacturer shall also recommend methods for testing for residual levels of the disinfectants. When disinfection is accomplished automatically by chemical disinfectant,

including ozone, or by high temperature procedures, activation of the disinfection system shall result in activation of a warning system and measures to prevent patient exposure to an unsafe condition.

If sodium hypochlorite (bleach) is used for cleaning or disinfecting the internal pathways of dialysis equipment, including but not limited to water treatment loops, concentrate containers, mixers, and delivery systems, the post rinse water residual level of free chlorine shall be as specified by the manufacturer's instructions.

4.2.2 Backflow prevention device

A backflow prevention device to isolate the water treatment system from the potable water supply according to local plumbing codes should be fitted to all water treatment systems.

4.2.3 Tempering valves

Tempering valves, if used, shall be sized to accommodate the anticipated range of flow rates of hot and cold water. They shall be fitted with a mechanism to prevent backflow of water into the hot and cold water lines and with a means to measure the outlet water temperature.

4.2.4 Sediment filters

Sediment filters should have an opaque housing or other means to inhibit proliferation of algae. Filters should be fitted with pressure gauges on the inlet and outlet water lines to measure the pressure drop, ΔP, across the filter.

NOTE Sediment filters are also known as multimedia or sand filters.

4.2.5 Cartridge filters

Cartridge filters should have an opaque housing or other means to inhibit proliferation of algae. Filters should be fitted with pressure gauges on the inlet and outlet water lines to measure the pressure drop, ΔP, across the filter.

4.2.6 Softeners

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. Automatic regeneration can be performed on a volume schedule or on a time schedule. For softeners that are regenerated automatically on a time schedule, the face of the timers used to control the regeneration cycle should be visible to the user. Operating controls shall be positioned so as to minimize inadvertent resetting.

4.2.7 Anion exchange resin tank

Anion exchange resin, sometimes referred to as an organic scavenger, can remove organic matter and other contaminants from the source water and protect carbon media from fouling, which can shorten its effective life for chlorine/chloramine removal. If an organic scavenger is installed to protect the carbon media, the scavenger should be installed upstream of the carbon beds. Anion exchange resins can also be used to remove contaminants that might otherwise foul the reverse osmosis membrane.

4.2.8 Carbon media

Carbon is used to remove small organic compounds, chlorine, and chloramine. At least one carbon bed or filter should be installed even if the water supply is from a well and no chlorine is present. Carbon removes organic contaminants from ground water, including solvents, pesticides, industrial wastes, and substances leaking from underground storage tanks. If chlorine is not present in the water, the carbon should be changed on a routine schedule. When carbon is used for the removal of chloramine, it

shall be adapted specifically to the maximum anticipated water flow rate of the system and the level of chloramine in the feed water.

Due to the risk of harm to a patient in the event of total chlorine breakthrough or organic contamination, the system shall be designed to prevent patient exposure to unsafe product water in the event of a single point failure. Protective measures can be incorporated into the system design through several means including:

— the use of two carbon beds in series with off-line sampling of product water from the first bed in each series (see off-line testing in ISO 23500-1:2019, 7.3.5). Each of the carbon beds shall have an EBCT of at least 5 min at the maximum product water flow rate (a total EBCT of at least 10 min);

— the use of redundant means of chloramines removal with off-line sampling of product water after the primary device (see off-line testing in ISO 23500-1:2019, 7.3.5). Possible alternatives include a granular activated carbon bed followed by a dense carbon block or two carbon block filters in series;

— the use of carbon systems used to prepare water for portable dialysis systems are exempt from the requirement for the second carbon and a 10 min EBCT, provided there is a redundant means of chloramine removal with off-line sampling after the primary device (see off-line testing in ISO 23500-1:2019, 7.3.5);

— the use of batch systems used to prepare water for portable dialysis systems are exempt from the requirement for the second carbon and a 10 min EBCT, provided there is a redundant means of chloramine removal with off-line sampling after batch production (see chlorine test methods in ISO 23500-1:2019, 7.3.5);

— the use of carbon media with duration or process volume limitation in conjunction with online surveillance of the product water and diversion of the product water to drain or a blocking valve with system shutdown, should the total chlorine level in the product water exceed 0,1 mg/l (see online testing in ISO 23500-1:2019, 7.3.5). Periodic testing of the online monitor and the frequency of the testing is specified per the system manufacturer's instructions. If an online monitor failure occurs, manual testing can be implemented to observe for chlorine and chloramines for 72 h similar to dual carbon designs as in ISO 23500-1:2019, B.2.5.

To avoid overly large beds, carbon beds are sometimes arranged as parallel sets, each set consisting of two beds in series. The beds are equally sized and water flows in parallel through each set. In this situation, each bed shall have a minimum EBCT of 5 min at the maximum flow rate through the bed. When parallel sets of beds are used, the piping should be designed to minimize differences in the resistance to flow from inlet and outlet between each parallel set of beds in order to ensure that water flows equally through all beds. A means shall be provided to sample the product water from the first bed in each series-connected pair and a sample port should be installed following the carbon beds for use in the event of total chlorine breaking through the first bed in a series-connected pair.

In situations where chloramine is not used to disinfect the water, and the ammonium [NH4+ formed by the protonation of ammonia (NH3)] level in the water is low, one carbon bed or a carbon cartridge filter with a shorter EBCT might be sufficient. Exhausted carbon media shall be discarded and replaced with new media according to a replacement schedule determined by regular surveillance. For example, with two beds, 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 replaced with a new bed, and the exhausted bed discarded.

Granular activated carbon with an iodine number greater than 900 is considered optimal for chlorine/chloramine removal. However, some source waters, such as those with a high organic content could require alternate 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 shall provide performance data to demonstrate that each adsorption bed has the capacity to reduce the total chlorine concentration in the feed water 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 shall not be used. Automatically backwashed carbon beds should be fitted with a mechanism

to prevent water containing chlorine or chloramine from entering the feed water line of downstream purification devices, such as reverse osmosis, while the carbon beds are being backwashed. For carbon beds that are backwashed automatically on a time schedule, the face of the timers used to control the backwash cycle should be visible to the user and the timer should be set so that backwashing occurs when dialysis is not being performed.

In some instances, activated carbon might not provide adequate removal of chloramine. Inadequate removal of chloramine can occur when the pH of the water is high, or when municipal water contains high levels of organic material or additives, such as orthophosphate for lead and copper control. Inadequate removal of chloramine can also appear to occur when naturally-occurring N-chloramines are present in the water. N-chloramines are relatively large molecules and are removed by reverse osmosis; however, they test positive in the assays used for chloramine, thus giving the impression of inadequate chloramine removal.

In these circumstances, other strategies for chloramine removal might be needed. One approach that has been used successfully is the injection of sodium bisulphite prior to the reverse osmosis system. Other approaches include installing anion exchange resin before the carbon beds to remove organic matter and other contaminants that might foul the activated carbon, or the injection of a mineral acid before the carbon beds to reduce the pH of alkaline feed water.

If carbon beds fitted with an online monitor for measuring total chlorine in the product water are used, there should be a means of preventing patient exposure to unsafe product water, such as the diversion of the product water to drain or a system shutdown, should the total chlorine level in the product water exceed 0,1 mg/l. Accompanying visual and/or audible alarms shall meet the relevant requirements of IEC 60601-1-8; for low-priority alarms if product water is diverted to drain or the system is shut down; otherwise, the alarms shall meet the relevant requirements of IEC 60601-1-8 for high priority alarms.

In addition, the sound emitted by the audible alarm shall be at least 65 dB (“A” scale) at 3 m and it shall not be possible to silence the alarm for more than 180 s. Alarms shall be situated so that they ensure a prompt response by personnel in the patient care area.

If the online monitor is placed between two carbon filters in series, a low-priority alarm can be accepted as long as manual surveillance is performed after the last filter or bed in the event of an alarm.

4.2.9 Chemical injection systems

Sodium bisulphite injected into the source water can be an effective means of reducing chlorine and chloramine concentrations. Ascorbic acid has also been used for this purpose. In addition, reducing the pH of alkaline feed water by the injection of mineral acids can enhance the efficiency of granular activated carbon. Chemical injection systems shall include a means of regulating the metering pump to control the addition of chemical. This control system shall be designed to tightly control the addition of chemical. The control system shall ensure that 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 observed parameter, such as pH, using an automated control system. If an automated control system is used to inject the chemical, there shall be an independent monitor of the controlling parameter. Monitors shall be designed so that the monitor cannot be disabled while a patient is at risk, except for brief, necessary periods of manual control with the operator in constant attention.

4.2.10 Reverse osmosis

When used to prepare water for haemodialysis applications, either alone or as the last stage in a purification cascade, reverse osmosis systems shall be shown to be capable, at installation, of meeting the requirements of 4.1, when tested with the typical feed water of the user, in accordance with the methods described in 5.1.

Reverse osmosis devices shall be equipped with online monitors that allow determination of product water conductivity and should be equipped with monitors that determine rejection rate based on conductivity. Monitors that display resistivity or total dissolved solids (TDS) could be used in place of conductivity monitors. Resistivity, conductivity, or TDS monitors shall be temperature-compensated,

generally to 25 °C. Monitors shall be designed so that the monitor cannot be disabled while a patient is at risk, except for brief, necessary periods of manual control with the operator in constant attention.

When a reverse osmosis system is the last chemical purification process in the water treatment system, it shall include a means of preventing patient exposure to unsafe product water, such as diversion of the product water to drain or system shutdown, in the event that the product water conductivity exceeds a pre-set limit. Accompanying audible alarms shall be at least 65 dB ("A" scale) at 3 m and it shall not be possible to mute the alarm for more than 3 min (180 s) following activation. Alarms shall be situated to ensure a prompt response by personnel in the patient care area.

4.2.11 Deionization

Deionization systems, when used to prepare water for haemodialysis applications, shall be observed continuously with a temperature-compensated [to 25 °C] monitor, to produce water of 1 MΩ·cm or greater specific resistivity (or conductivity of 1 µS/cm (0, 1 mS/m) or less). The monitor used, shall be designed so that it cannot be disabled while a patient is at risk, except for brief, necessary periods of manual control with an appropriately trained operator in constant presence.

An audible and visual alarm shall be activated when the product water resistivity falls below 1 MΩ·cm and the product water stream shall be prevented from reaching any point of use, by being diverted to a drain. Accompanying audible alarms shall be at least 65 dB ("A" scale) at 3 m and it shall not be possible to mute the alarm for more than 3 min (180 s) following activation. Alarms shall be situated to ensure a prompt response by personnel in the patient care area.

Feed water for deionization systems shall 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 shall be followed by an endotoxin retentive filter or other bacteria- and endotoxin-reducing device.

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

4.2.12 Bacteria and endotoxin retentive filters

When bacteria and endotoxin retentive filters are used in a water treatment system for haemodialysis applications, the manufacturer of the filter shall disclose the performance of the filter and the conditions under which that performance can be obtained. It is recommended that filters be configured in a cross-flow mode. However, dead-end filters that have validated endotoxin and bacterial removal characteristics can also be used.

Endotoxin retentive filters should have an opaque housing or other means to inhibit the growth and proliferation of algae. Endotoxin retentive filters should be fitted with a means of assessing filter integrity and fouling, such as surveillance of the pressure drop, ΔP, across the filter using pressure gauges on the inlet and outlet water lines.

4.2.13 Storage and distribution of dialysis water

4.2.13.1 Piping systems

The dialysis water distribution system shall not contribute chemicals (such as aluminium, copper, lead and zinc) or bacterial contamination to the product water. Dialysis water distribution systems should be designed to minimize bacterial proliferation and biofilm formation, such as by using a continuous recirculation loop with flow in the return line. Areas of stagnant flow (dead zones) in the loop system shall be avoided. Direct feed systems shall include a means of verifiably preventing retrograde flow of water into the distribution loop from the feed side of the reverse osmosis unit.

4.2.13.2 Storage tanks

When used, storage tanks should have a conical or bowl-shaped base and should drain from the lowest point of the base. Bladder tanks and pressurized surge tanks should not be used in the dialysis water distribution system. Storage tanks should have a tight-fitting lid and be vented through a hydrophobic 0,45 µm or less air filter. Sight tubes should be avoided due to the possible growth of algae and fungi. If an overflow pipe is used, it shall be fitted with a means of preventing contamination. Means shall be provided to effectively disinfect any storage tank installed in a dialysis water distribution system. An endotoxin retentive filter, or some other form of microbial control device, should be installed distal to the storage tank.

4.2.13.3 Ultraviolet irradiators

When used to control bacterial proliferation in dialysis water storage and distribution systems, UV irradiation devices shall emit light at a wavelength of 254 nm and provide 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 shall be sized for the maximum anticipated flow rate according to the manufacturer's instructions. UV irradiators should be followed by an endotoxin retentive filter.

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

To prevent the use of sub lethal doses of radiation that could lead to the development of resistant strains of bacteria, UV irradiators shall 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 irradiation source should be replaced. Alternatively, the irradiation source 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 a 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. The required energy depends on whether sterilization or bacteriostasis is aimed for.

NOTE The recommendations provided in this clause concern UV irradiators used specifically for bacterial control. UV irradiators also can be used for other applications in a water treatment and distribution system. If an ultraviolet irradiator is utilized for reduction of chlorine or chloramine as an adjunct to carbon media, it is important that the manufacturer verifies the performance of the device and supplies instructions regarding minimum radiant energy and wavelength for continuing performance.

4.2.13.4 Hot water disinfection systems

When used to control bacterial proliferation in water treatment, storage, and distribution systems, the water heater of a hot water disinfection system shall be capable of delivering hot water at the temperature and for the exposure time specified by the manufacturer. Hot water disinfection systems should be equipped with a surveillance system that indicates if the temperature at the point farthest from the water heater drops below the manufacturer's recommended minimum temperature during the disinfection cycle. When disinfection is accomplished automatically by high temperature procedures, activation of the disinfection system shall result in activation of a system indicating that disinfection is in process. Operating controls should be positioned so as to minimize inadvertent resetting.

NOTE For dialysis water distribution loops, the point farthest from the water heater is where the water re-enters the storage tank (indirect feed systems) or where the water returns to the reverse osmosis system (direct feed systems).

4.2.13.5 Ozone disinfection systems

When used to control bacterial proliferation in dialysis water storage and distribution systems, an ozone disinfection system shall be capable of delivering ozone at the concentration and for the exposure

time specified by the manufacturer. 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, is capable of killing bacteria, bacterial spores, and viruses in water. Following sanitation, the residual ozone level should be reduced to less than 0,1 mg/l.

When ozone disinfection systems are used, surveillance of the ambient air ozone levels in the area of the ozone generator shall be performed to ensure conformity with exposure limits established by the appropriate health and safety organization.

Activation of an ozone disinfection system shall result in activation of a system to indicate that disinfection is in process and in the activation of measures to prevent patient exposure to an unsafe condition. Operating controls shall be positioned so as to minimize inadvertent resetting.

5 Testing

5.1 Conformity with dialysis water quality requirements

5.1.1 General

This clause defines test methods by which conformity with the requirements of Clause 4 shall be verified.

NOTE The test methods listed do not represent the only acceptable test methods available but are intended to provide examples of acceptable methods. Methods other than those stated can be used provided that they have been appropriately validated and are comparable to established test methods.

The requirements of ISO 23500-3; apply to the dialysis water as it enters the equipment used to prepare concentrates from powder at a dialysis facility, to prepare dialysis fluid, or to reprocess dialysers. As such, these requirements apply to the water treatment system as a whole and not to each of the individual devices that make up the system. However, collectively, the individual devices shall produce water that meets the requirements of ISO 23500-3: when provided with potable water as received at the facility or dialysis clinic. Tests for conformity with water quality requirements should be performed when the system is operating under stable conditions representing normal operation.

5.1.2 Microbiology of dialysis water

Samples shall be collected immediately prior to where the water re-enters the storage tank in an indirect feed system or immediately prior to where the water returns to the reverse osmosis system in a direct feed system. Additional samples shall be collected at, or immediately prior to, the point where water enters the equipment used to prepare concentrates or reprocess dialysers if the line supplying that equipment with water is separate from the distribution loop supplying the dialysis machines.

Samples should be analysed as soon as possible after collection to avoid unpredictable changes in the microbial population. If samples cannot be analysed within 4 h of collection, they should be stored at <10 °C without freezing until ready to transport to the laboratory for analysis. Sample storage for more than 24 h should be avoided, and sample shipping should be in accordance with the laboratory's instructions.

Total viable counts (standard plate counts) shall be obtained using the membrane filter technique, spread plates, or pour plates. The calibrated loop technique shall not be used.

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

Recommended methods and cultivation conditions are Tryptone Glucose Extract Agar (TGEA) and Reasoner's Agar No. 2 (R2A) incubated at 17 °C to 23 °C for a period of 7 days and tryptic soy agar (TSA) at an incubation temperature of 35 °C to 37 °C and an incubation time of 48 h, see ISO 23500-3:2019, Table 3. The rationale for the inclusion of TSA is detailed in ISO 23500-3:2019, A.4.

Different media types and incubation periods can result in varying colony concentrations and types of microrganisms recovered. The use of Reasoner's 2A agar (R2A) has been reported to result in higher colony counts than tryptic soy agar (TSA) in water samples and dialysis fluids. [7][8] In a more recent publication the authors indicated that there were no significant differences for comparisons of bacterial burden in the proportion of standard water and standard dialysis fluid yielding colony counts ≥50 CFU/ml when assayed using R2A and TSA at the conditions stated above when used for indicating microbial burden in samples taken from water used for standard dialysis and standard dialysis fluid. [6] Tryptone glucose extract agar (TGEA) has also been reported to yield higher colony counts than TSA. [8] Maltais et al. in their comparison of this medium with TSA when quantifying the microbial burden in water and dialysis fluid used for standard dialysis also showed that the proportion of water samples yielding colony counts ≥50 CFU/ml quantified using TGEA incubated at 17 °C to 23 °C for a period of 7 days 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 the microbial burden was ≥50 CFU/ml were not significantly different when comparing the TGEA and TSA methods. [6]

The user should determine which of these methodologies is appropriate for the circumstance, taking into account the advantages of each.

According to the United States Pharmacopeia, "the decision to use longer incubation times, should be made after balancing the need for timely information and the type of corrective actions required when alert or action level is exceeded with the ability to recover the microorganisms of interest. The advantages gained by incubating for longer times namely recovery of injured microorganisms, slow growers, or more fastidious microorganisms, should be balanced against the need to have a timely investigation and take corrective action, as well as the ability of these microorganisms to detrimentally affect products or processes" (e.g. patient safety) [9].

Alternative incubation conditions and colony counting times can be used if they have been appropriately validated and proven to be comparable to the recommended methods and cultivation conditions in ISO 23500-3:2019, Table 3. Blood agar and chocolate agar shall not be used.

Currently there are no requirements for routine surveillance for the presence of fungi (i.e yeasts and filamentous fungi) which might co-exist with other microbial species, however if indication of their presence is required, membrane filtration is the preferred method for the provision of a sample suitable for analysis. Culture media used should be Sabouraud or Malt Extract Agar (MEA) with a 7 d incubation period at 20 °C to 22 °C. Alternate techniques validated against Sabouraud Malt Extract Agar, with a 7 d incubation period at 20 °C to 22 °C, can also be used provided it has been demonstrated that such methods have been appropriately validated and are comparable to the cited methods.

Endotoxin concentrations shall be determined by a LAL assay or another validated test method.

5.1.3 Maximum level of chemical contaminants

Chemical analyses of the water contaminants listed in ISO 23500-3:2019, Table 1 (reproduced as Table B.1) can be obtained by using methods referenced by the American Public Health Association[10], methods referenced by the US. Environmental Protection Agency[11], methods referenced in applicable pharmacopoeia, or other appropriately validated and comparable analytical methods.

Conformity with the requirements listed in ISO 23500-3:2019, Table 2 (reproduced as Table B.2) shall be shown in one of three ways.

— Where such testing is available, the individual contaminants in ISO 23500-3 :2019, Table 2 can be determined using chemical analysis methods referenced by the American Public Health Association[10], methods referenced by the US. Environmental Protection Agency[11], methods referenced in applicable pharmacopoeia, or other appropriately validated and comparable analytical methods.

— Where testing for the individual trace elements listed in ISO 23500-1:2019, Table 2 is not available and the source water can be demonstrated to meet the standards for potable water as defined by

the WHO[5] or local regulations, an analysis for total heavy metals can be used with a maximum allowable level of 0,1 mg/l.

— If neither of these options is available, conformity with the requirements of ISO 23500-1:2019, Table 2 can be met by using water that can be demonstrated to meet the potable water requirements of the WHO or local regulations and a reverse osmosis system with a rejection of >90 % based on conductivity, resistivity or TDS.

Samples shall be collected at the end of the water treatment cascade or at the most distal point in each water distribution loop.

5.2 Conformity with water treatment equipment requirements

5.2.1 General

5.2.1.1 Water treatment system

The need for tests to determine the quality of water used to feed water treatment equipment is dependent upon specific features of the devices. Suppliers of water treatment devices should select and perform such tests (e.g. iron, pH, silica, total dissolved solids, alkalinity, and total hardness) as are necessary to ensure the reliable performance of their devices.

5.2.1.2 Materials compatibility

Biocompatibility testing should begin with a risk analysis. Using the results of that risk analysis, a testing rationale should be developed using, for example, methods described in applicable pharmacopoeia or other appropriate documents.

5.2.1.3 Regenerated or reconstituted devices

The adequacy of disinfection procedures can be demonstrated by culturing a sample of the device's product water following the disinfection procedure. Where regenerated or reconstituted devices are provided by a vendor as medical devices, the disinfection and intermixing requirements of 4.2.1.3 may be demonstrated by confirmation that the device has been disinfected using validated procedures during regeneration or reconstitution and that validated procedures have been used to ensure that the devices and their component parts have been kept separate from devices and component parts used in non-potable water applications.

5.2.1.4 Disinfection protection

Conformity with the requirements of 4.2.1.4 for chemical disinfection procedures may be determined by testing for the disinfectant in the product water at the end of the disinfection procedure. If a commercially available chemical disinfectant, such as peracetic acid, is used, an established test for residual disinfectant shall be used according to the test manufacturer's instructions, and the residual level shall be that recommended by the manufacturer of the specific disinfectant.

When formaldehyde is used, residual levels can be determined by the Hantzsch reaction, Schiff's reagent, or by an equivalent test. Residual levels shall not exceed 3 mg/l or that stated in local requirements.

When using sodium hypochlorite for disinfection, the residual level should be that recommended by the manufacturer.

Conformity with the requirements of 4.2.1.4 for high-temperature disinfection shall be shown by demonstrating that the product water has returned to a safe temperature.

Conformity with the requirements of 4.2.1.4 for ozone disinfection shall be shown by demonstrating that the ozone concentration in the product water has returned to a safe level (less than 0,1 mg/l).

Conformity with the patient protection requirements of 4.2.1.4 shall be demonstrated by inspection.

5.2.2 Backflow prevention devices

Conformity with the requirements of 4.2.2 shall be determined by visual inspection.

5.2.3 Tempering valves

Conformity with the requirements of 4.2.3 shall be determined by visual inspection and review of manufacturer's specifications.

5.2.4 Sediment filters

Conformity with the requirements of 4.2.4 shall be determined by visual inspection.

5.2.5 Cartridge filters

Conformity with the requirements of 4.2.5 shall be determined by visual inspection.

5.2.6 Softeners

Conformity with the requirements of 4.2.6 shall be determined by inspection.

5.2.7 Anion exchange resin tanks

The performance of anion exchange resin tanks may be checked by periodically testing the feed and product water for total organic carbon (TOC) or tannins. Proper regeneration of the resin tank may be determined by observing salt usage and regeneration timer settings.

5.2.8 Carbon media

Total chlorine removal may be used as an indication of carbon capacity. A DPD test kit selected for this purpose or a similar method shall be used to detect breakthrough of total chlorine, carbon exhaustion, or both. DPD materials shall be those designed for total chlorine detection and shall be used according to manufacturers' instructions. Alternatively, online monitors or “dip and read” test strips based on Michler's thioketone (MTK) may be used to measure the concentration of total chlorine. Tests for both free and total chlorine may also be performed to determine if chloramine is present. The difference between total chlorine and free chlorine is combined chlorine, which shall be considered chloramine. The utility of any test is dependent upon the sensitivity and detection limits of the analytical method used. Tests for total chlorine in product water shall have a sensitivity of at least 0,1 mg/l. Alternative tests (e.g. titrometry) should be used to follow up questionable results. Tests are not required for organic or radioactive materials.

Conformity with the configuration requirements of 4.2.8 shall be determined by inspection.

NOTE In some instances, activated carbon might not provide adequate removal of chloramine. Inadequate removal of chloramine might occur when the pH of the water is high, or when municipal water contains high levels of organic material or additives, such as orthophosphate for lead and copper control. Inadequate removal of chloramine might also appear to occur when naturally-occurring N-chloramines are present in the water. N-chloramines are relatively large molecules and are removed by reverse osmosis; however, they test positive in the assays used for chloramine, thus giving the impression of inadequate chloramine removal. In these circumstances, other strategies for chloramine removal might be needed. One approach that has been used successfully is the injection of sodium bisulphite prior to the reverse osmosis system. Other approaches include installing anion exchange resin before the carbon beds to remove organic matter and other contaminants that might foul the activated carbon, or the injection of a mineral acid before the carbon beds to reduce the pH of alkaline feed water.

Conformity with the configuration requirements of 4.2.8 shall be determined by inspection.

5.2.9 Chemical injection systems

Conformity with the requirements of 4.2.9 shall be determined by inspection.

5.2.10 Reverse osmosis

Conformity with the performance requirement of 4.2.10 shall be determined by the tests of 5.1.2 and 5.1.3.

Conductivity, resistivity, or TDS measurements of product water of reverse osmosis devices can be accomplished by using conventional monitors that incorporate temperature compensation features. Conformity with this requirement and the other configuration requirements of 4.2.10 shall be determined by inspection.

5.2.11 Deionization

Resistivity measurements for product water of deionizers can be accomplished using conventional resistivity cells that incorporate temperature compensation features. The presence of required safety systems can be verified by inspection.

5.2.12 Endotoxin retentive filters

Conformity with the requirements of 4.2.12 shall be shown using the test methodologies for determining bacteria and endotoxin given in 5.1.2.

5.2.13 Storage and distribution of dialysis water

5.2.13.1 Piping systems

The absence of copper, lead, and zinc and the configuration of a water treatment device or system can be determined by visual inspection. Non-contribution of bacteria and specific chemical contaminants to the water by the distribution system can be verified by using the tests described in 5.1.2 and 5.1.3.

5.2.13.2 Storage tanks

Conformity with the requirements of 4.2.13.2 shall be determined by visual inspection.

5.2.13.3 Ultraviolet irradiators

Conformity with the requirements of 4.2.13.3 shall be determined by visual inspection.

5.2.13.4 Hot water disinfection systems

Conformity with the requirements of 4.2.13.4 shall be determined by measuring water temperatures in the fluid pathway being disinfected at the most distal point for the disinfection time specified by the manufacturer.

Conformity with the configuration requirements of 4.2.13.4 shall be determined by inspection.

5.2.13.5 Ozone disinfection systems

Conformity with the requirements of 4.2.13.5 shall be determined by using an online monitor for dissolved ozone or by analysis of water samples using test kits based on indigo trisulfonate or DPD chemistry.

Conformity with the configuration requirements of 4.2.13.5 shall be determined by inspection.

6 Labelling

6.1 General

The term “labelling”, as used in this document, includes any written material accompanying any water treatment device or system, such as instructions for use and operator's manuals, or any instructions or control feature markings attached to the device or system.

6.2 Device markings

The following information shall accompany each water treatment device or system. Items a) to c) shall be directly affixed to the device or system or, in the case of disposable elements, to the immediate packaging, whereas items d) to f) can be provided in accompanying product literature.

a) Name and address of manufacturer;

b) Trade name and type of device;

c) Model and serial number;

d) A warning that product literature should be read before use (if appropriate);

e) Prominent warnings about substances (e.g. germicides) needing to be removed from the device before using the product water for dialysis;

f) Identification of fitting type or specification when necessary to prevent improper connections.

6.3 Product literature

The manufacturer shall provide literature to each user which contains, but is not necessarily limited to, the following information.

a) Warnings that selection of water treatment equipment for dialysis is the responsibility of the user and that product water should be tested periodically.

b) A description of the device or system, including a list of monitors, alarms, and ancillary devices provided as standard equipment.

c) A schematic diagram of the device or system showing the location of any valves, online monitors, or sampling ports.

d) Operating specifications, such as maximum and minimum input water temperature, pressure and flow rate, limits on input water quality, pressure of product water at various flow rates, and maximum output of product water.

e) Detailed instructions for use, including initial start-up, testing, and calibration, operation and meaning of alarms, operational adjustments to monitors, alarms and controls, and connections to other equipment.

f) For systems, the minimum quality of feed water required for the system to produce dialysis water meeting the chemical requirements of this document.

g) For systems, a warning that although a water treatment system produces water of sufficient quality to meet the requirements of this document, distribution of that water could degrade its quality to the point where it no longer meets the requirements of the document if the distribution system is not maintained appropriately.

h) Safety features and warnings concerning the consequences if these features are circumvented.

i) Information pertaining to online monitors of water quality, including operational factors that could affect monitor performance (e.g. temperature).

j) In the case of systems whose product water is proportionally related to feed water quality, warnings that feed water quality shall be monitored. Since changes in product water could exceed acceptable limits if feed water deteriorates significantly, the user is responsible for surveillance.

k) In the case of activated carbon beds, a warning that exhausted or contaminated carbon should be discarded and replaced with new beds.

l) For devices regenerated or reconstituted offsite, instructions on how to safely reconnect the device to the water treatment system and how to remove any contaminant or disinfectant in the device before use.

m) A statement on regenerated or reconstituted devices, such as deionizers, confirming that there was no intermixing of regenerated or reconstituted devices returned from medical or potable water users and devices returned from process or non-potable water users. A statement that a description of the methods used to ensure that no intermixing occurred is available on request.

n) For automatically regenerated water treatment devices, identification of the mechanism (for example, lock-out valves) that prevents excessive levels of contaminants entering the product water during regeneration.

o) In the case of deionizers, a warning that deionizers should be preceded by an activated carbon bed and a recommendation that they be followed by an endotoxin retentive filter or other bacteria- and endotoxin-reducing device.

p) In the case of ultraviolet (UV) irradiators, a requirement that the manufacturer disclose the effectiveness of the device in killing specific bacteria under specified operating conditions and a recommendation that UV irradiators be followed by an endotoxin retentive filter or other bacteria- and endotoxin-reducing device.

q) In the case of hot water disinfection systems, a requirement that the manufacturer disclose the effectiveness of the system in killing specific bacteria under specified operating conditions.

r) In the case of ozone disinfection systems, a requirement that the manufacturer disclose the effectiveness of the system in killing specific bacteria under specified operating conditions and that he provide a warning that product water shall not be used until the minimum time required for ozone to dissipate has elapsed.

s) In the case of hot water disinfection systems, a warning that appropriate heat-resistant materials be used for the fluid pathways to be disinfected with hot water.

t) In the case of ozone disinfection systems, a warning that appropriate ozone-resistant materials be used for the fluid pathways to be disinfected with ozone.

u) Materials of construction that are in contact with water, identified generically.

v) Typical life expectancy, capacity, or indication of the end of life of devices that are non-durable or require periodic regeneration or reconstitution and a statement that additional information on device life expectancy or capacity relative to the user's typical feed water is available upon request. In the case of carbon beds, manufacturers or suppliers should provide a warning that unexpected exhaustion could occur because of variable feed water characteristics. The only safeguard against such unforeseeable eventuality is diligent surveillance of carbon filter effluent by the user.

w) Specified water supply or operating conditions that could cause the device to fail.

x) Information about germicides and cleaning agents known to be compatible with materials used in the device, as well as information about chemicals with which materials used in the device are incompatible.

y) If applicable, a method of cleaning and disinfecting the equipment, and of removing residual germicide, so that the system of which the equipment is part is capable of meeting the requirements for microbial and endotoxin contamination given in 4.1.4.

z) Other maintenance and service instructions, including recommended preventive maintenance procedures and schedules, recommended surveillance schedules, troubleshooting guidelines intended for the user, service information, a recommended spare parts list, and a warning of the consequences if maintenance instructions are not followed.

aa) A warning that if, after installation and subsequent use, any device in the water treatment system is changed or replaced, the user should conduct appropriate tests to ensure that the revised system meets the initial design criteria.

bb) Information on storage, if allowed, of devices while not in use, including appropriate packing chemicals, storage conditions, and duration.

Annex A
(informative)

Rationale for the development and provisions of this document

A.1 Scope

The items included within the scope of this document are equipment used to treat water for the preparation of concentrates and dialysis fluid, or for the reprocessing of dialysers for multiple uses, and the devices used to store and distribute this water.

This document seeks to prevent the use of options that are hazardous to patients treated with haemodialysis and related therapies. For example, this document is needed to prevent adverse effects to the patient caused by formulation of dialysis fluid with water that contains high levels of certain contaminants.

Water treatment and distribution systems incorporate a variety of devices that can be provided and installed by different vendors, making it difficult to assign responsibility for conformity with this document to any one individual or company. To address this concern, primary responsibility for conformity with this document has been placed on the individual or company that specifies the water treatment and distribution system installed in a given situation. Responsibility could also lie with the vendor who assembles and installs the system and with the manufacturer of any individual device of the water treatment and distribution system if that manufacturer specifies that their device is intended for haemodialysis applications. Additionally, the physician in charge of dialysis should have a sufficient understanding of water treatment for haemodialysis to critically appraise the system. This is essential, as they have ultimate responsibility for the care of the patient and for ensuring that the dialysis fluid is formulated correctly and meets the requirements of all applicable standards.

A.2 Requirements

A.2.1 Dialysis water quality requirements

A.2.1.1 General

Individual water treatment devices might not provide water that meets the requirements of this document in its entirety. ISO 23500-3:2019 gives the requirement that a water system be maintained in a condition to continually meet the defined water quality without giving a method of accomplishing the requirements. This document is directed at the manufacturer of the dialysis water treatment systems and defines the requirements that the manufacturer should meet prior to the user assuming responsibility for the water system. However, manufacturers of individual water treatment devices should be aware of the requirements for the final dialysis water and that they should be prepared to recommend other water treatment devices that might need to be used in conjunction with their device to produce water which meets the requirements of this document.

A.2.1.2 Chemical contaminants

The rationale for the chemical contaminant requirements is set forth in Annex A of ISO 23500-3:2019.

Compounds indicated in Annex B (Tables B.1 and B.2) should not be taken as a definitive list of harmful substances, but as a partial listing of those that might reasonably be expected to be present and have clinical implications.

In addition to these substances which are known to harm haemodialysis patients, the World Health Organization lists guideline values for drinking water for 82 known toxic chemical contaminants, including organic substances[5]. Hazards associated with the presence of organic compounds, such as pesticides, polycyclic aromatic hydrocarbons and other chemicals such as pharmaceutical products and endocrine disruptors for haemodialysis patients are difficult to define and are probably of a long-term nature, furthermore their measurement on a routine basis is costly. Accumulation of pesticides has been demonstrated in uraemia and can be associated with toxic side-effects[12]. The presence of pharmaceuticals and endocrine disrupting compounds (EDCs) in the environment raises many questions about risk to the environment and risk to human health. Researchers have attributed adverse ecological effects to the presence of these compounds, particularly EDCs, though there is no consensus on what risk, if any, these compounds pose to human health[13].

The ability of a water treatment system to remove organic contaminants depends mostly on the structure and concentration of the contaminant. Chemical oxidation, biological removal/transformation, or nanofiltration/reverse osmosis are the technologies most commonly used for pharmaceutical and endocrine disruptor removal. [13] [14] Granular activated carbon (GAC) is highly effective at removing the majority of organic contaminants in water. However, break-through curves demonstrated that compounds with greater hydrophilicity breach activated carbon faster than hydrophobic compounds and backwashing cycles play an important role. [15] As activated carbon is usually used in the dialysis water treatment setting for the removal of chlorine and chloramine, consequently if it is also to be used for organic compound removal, it shall be appropriately sized, since carbon valences can be already occupied and therefore not available for removal.

Currently, dialysis related standards and guidelines do not specify recommendations or maximum allowable levels for organic compounds in dialysis water. The starting point to establish whether organic compounds are a cause for concern is the national drinking water requirement for such compounds. If there is evidence that organic compounds in the feed water are above that permitted in drinking water, the appropriate dimensioning of the Granulated Activated Carbon (GAC) to reduce the levels to those for drinking water should be undertaken.

Iron is not included because it does not enter the patient's blood in sufficient quantities to cause toxicity. Iron can, however, cause fouling of water treatment devices or dialysis fluid supply systems. While a specific limit has not been set, water treatment equipment suppliers are encouraged to consider the iron content of the feed water when recommending suitable equipment. Generally, to bind iron and manganese to avoid the staining of fixtures and clothing, formulated phosphates (known as polyphosphates) are added to drinking water. The presence of such compounds, could cause significant problems in water treatment. To establish if this is likely to be a problem, information from the water provider should be sought at the earliest opportunity.

To minimize bacterial content in potable water, which forms the starting point of water treated for dialysis applications, chlorine or chloramine in the form of monochloramine are added. Chlorine dioxide may also be used as an alternate. The level of these compounds in potable water, has been set so that no adverse health effects arise from normal water intake (4 mg/l or 4 ppm as an annual average for chlorine and chloramine, and 0,8 mg/l or 800 ppb for chlorine dioxide). The levels, for chlorine and chloramine however pose risks to the patient receiving dialysis, and consequently maximum limits for dialysis water in respect of chlorine and chloramine have been set . Total chlorine is defined as the sum of free and combined chlorine. Total chlorine maximum allowable level is: 0,1 mg/l.

Whereas maximum limits for chlorine and chloramine in dialysis water have been set in accordance with clinical experience, a maximum limit for chlorine dioxide, which breaks down in water to yield chlorite, chlorate, and chloride ions has not been set. Currently, there is little information available to the potential health hazards associated with exposure to chlorine dioxide. A published study confined to 17 patients unknowingly treated with water prepared by carbon and reverse osmosis from water disinfected with chlorine dioxide showed no evidence of adverse effects when, the water used to prepare dialysis fluid contained 0,02 mg/l to 0,08 mg/l of chlorite ions and no detectable chlorate ions[16]. However, in this study the patient population was small and potentially important haematological parameters were not measured. Furthermore, there were only sparse data included on the removal of chlorine dioxide, chlorite ions, and chlorate ions by carbon and reverse osmosis, and it was not clear if sufficiently sensitive methods were available for analysis. In view of this limited and

incomplete information, the working group has not set maximum allowable levels of chlorine dioxide, chlorite ions, or chlorate ions in water to be used for dialysis applications or make recommendations on methods for their removal. However, in specifying water treatment systems, manufacturers of such systems should be aware of the possibility that chlorine dioxide may at some point be used to control microbial contamination in the water.

Water supplied to renal units may be via a direct feed to the water treatment plant from the public supply (direct feed), or it may form part of a supply and distribution network of a building such as a hospital or clinic (indirect feed). When the water does not come via a direct feed, there should be awareness that antimicrobial agents such as silver stabilized hydrogen peroxide, or chlorine dioxide may be added locally to suppress the growth of legionella in the distribution network of the building. Haemolysis can result from residual hydrogen peroxide left in dialysis water storage and distribution systems after disinfection with hydrogen peroxide and inadequate rinsing leading to clinical complications[17][18].

A.2.1.3 Microbiological contaminants

The supplier of water treatment equipment is responsible for recommending a method of cleaning the equipment so that dialysis water meeting the microbial requirements of ISO 23500-3 can routinely be produced when typical feed water is presented. Beyond this qualification, it becomes the responsibility of the user of the system to observe the system for on-going conformity in accordance with ISO 23500-5 :2019. The rationale for such surveillance forms part of ISO 23500-3 :2019.

A.2.2 Water treatment equipment requirements

A.2.2.1 General

A.2.2.1.1 Water treatment system

The supplier of the complete water treatment system is responsible for assuring that the water produced by the system can routinely meet the maximum allowable chemical contaminant levels specified in ISO 23500-3 and summarized in Tables B.1 and B.2, or the prescription of the physician, at installation. Beyond this qualification, it becomes the responsibility of the physician in charge of dialysis to observe the system to ensure that the treatment device or devices maintain an acceptable level of purity of the water. Variations in water quality or the presence of as-yet-unidentified toxic substances will obviously compromise the system's safety. Such variations typically do occur, and while the supplier cannot be held accountable for the performance of the water treatment system during such variations, selection of water purification equipment should include careful consideration of methods to cope with such changes, many of which can be anticipated through consultation with the provider of water.

The responsibility for the selection and use of water treatment devices on the basis of the supplier's recommendations, may rest with an individual or number of individuals working collectively. The physician in charge of dialysis has the ultimate responsibility for the clinical care of the patient as well as responsibility for ensuring that the dialysis fluid produced using water that has been treated meets the requirements of all applicable quality standards. Consequently the physician in charge of dialysis should form part of the selection or decision making process. This person, should understand enough about water treatment to critically appraise the system under consideration. If the selected system does not provide an adequate margin of safety due to variability in the quality of water used to feed the water treatment system, then the supplier should recommend additions to the system or alternative systems that would address this. Continued surveillance of the water supply is necessary to maintain treatment methods consistent with safety.

A.2.2.1.2 Materials compatibility

Non-toxicity of construction materials for haemodialysis water treatment equipment is of major importance. Some well-recognized non-toxic materials include certain stainless steel formulations, silicon rubber, borosilicate glass, polypropylene, polyvinylchloride (PVC), chlorinated PVC (CPVC), polyvinylidene fluoride (PVDF), polyethylene, cross-linked polyethylene (PEX), and polytetrafluorethylene (PTFE). Data are now available that demonstrate that materials once regarded

as inert can in fact be toxic in this application (e.g. copper leaches from copper conduits, especially in the presence of low pH, which can occur when a deionizer is exhausted). Other materials have been documented as being hazardous to the patient (e.g. brass, zinc, iron, and aluminium), and these materials should also be avoided. The hidden hazard with respect to construction materials derives from long-term cumulative toxicity. Haemodialysis is a long-term chronic treatment modality, and this fact should be acknowledged when selecting construction materials. A risk analysis according to ISO 14971:2007 should be used to establish the suitability of materials based on existing data. If that analysis suggests the need for additional testing, that testing should be based on the approaches outlined in the ISO 10993 series of standards. Users of this document shall be aware of the requirements of those standards.

Repeated exposure to ozone or hot water might have a deleterious effect on some plastic or metal materials. Therefore, manufacturers are required to include warnings that only ozone- or heat-compatible materials be used in piping systems intended for use with ozone or hot water disinfection devices, respectively [see 6.3 s) and 6.3 t)].

A.2.2.1.3 Regenerated or reconstituted devices

Regenerated or reconstituted devices are subject to bacterial contamination that can cause excessive bacterial counts in product water (see 4.1.4). Disinfection procedures are required to minimize this risk. When devices are regenerated at a central facility, there is a risk of cross-contamination and improper disinfection and rinsing[19]. Some exchange-type deionizers are used for both dialysis and industrial recovery of plating metals, such as chromium and silver, from effluent process water. In some regeneration facilities, resins from both processes or non-potable users and from medical or potable users are regenerated together as a batch. Traces of these toxic metals will remain bound to the resins and could be eluted into water during subsequent use. For that reason, such mixed use is prohibited in this document.

A.2.2.1.4 Disinfection protection

Disinfection procedures can render product water unsafe because of toxic chemicals or excessive temperatures. Therefore, provision was made for restoring the water treatment system to a safe condition after disinfection. Although the user is responsible for carrying out manual disinfection procedures, the manufacturer should demonstrate that recommended disinfection procedures meet the requirements of 4.2.1.4.

A.2.2.2 Backflow prevention device

A backflow prevention device isolates the water treatment system from the potable water supply, thereby protecting the potable water system from possible contamination in the event of a sudden reduction in pressure in the potable water supply.

A.2.2.3 Tempering valves

The performance of many water treatment devices is temperature sensitive. In less temperate climates, seasonal fluctuations in cold water temperature could impact the performance of these devices. A tempering valve can be used to blend hot and cold water to provide a constant feed water temperature independent of any seasonal changes in feed water temperature. Excessive water temperatures resulting from malfunction of a tempering valve can damage downstream devices, including reverse osmosis membranes and plastic pipes and pipe fittings. For that reason, consideration was given to requiring that tempering valves be fitted with a water temperature monitor that activates an audible alarm in the event that a high temperature is sensed. While recognizing the potential for equipment to be damaged by hot water, no consensus could be reached on the need for such a requirement.

A.2.2.4 Sediment filters

Accumulation of organics, bacteria, and algae in filters can lead to proliferation of bacteria to the point of overloading downstream devices or producing dangerous endotoxin levels. Use of opaque housings to reduce the light that promotes algae growth and differential pressure surveillance can reduce this risk.

A.2.2.5 Cartridge filters

Accumulation of organics, bacteria, and algae in filters can lead to proliferation of bacteria to the point of overloading downstream elements or producing dangerous endotoxin levels. Use of opaque housings to reduce the light that promotes algae growth and differential pressure surveillance can reduce this risk. 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 growth when the filter cartridges are changed. For this reason, 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.

A.2.2.6 Softeners

The process by which "hard" water (containing high levels of calcium and magnesium) is made "soft", involves the exchange of sodium ions for the calcium and magnesium in the water supply. The resin should be regenerated with brine to sustain capacity for exchange. Regeneration can be either manual or automatic with a timer. During regeneration, excess sodium can enter the product water stream if there is a temporary interruption of power, a malfunction in regeneration control, or inadequate water pressure. There are no monitors on a softener to detect excess sodium in the product water stream, and the physiological effects of excess sodium in the patient are severe[20]. Therefore, protection against such excessive levels of sodium, as might occur during regeneration of a water softener, is required. An automatic bypass valve most easily provides this protection during the regeneration cycle.

A.2.2.7 Anion exchange resin tank

High levels of organic matter in the source water might foul carbon media. Organic molecules (usually very large) are attracted to carbon and become attached at the pore sites, effectively blocking the pore and sealing off the surface area within that pore. As organic molecules accumulate on the surface of the carbon, there is less surface area available for removal of chlorine. Organic scavengers operate similar to a water softener, exchanging anions and organic matter for chloride ions. Source water testing for organics (TOC or tannins) might indicate if an organic scavenger will help protect carbon media.

A.2.2.8 Carbon media

Carbon beds are particularly prone to bacterial growth because of their porosity and affinity for organics. More stringent requirements for the installation of carbon beds and their surveillance are included because of continued reports of clusters of haemolysis related to insufficient removal of chloramine from municipal water supplies[22][23]. Public health measures designed to eliminate lead and copper from tap water have reinforced the need for careful surveillance of carbon beds because the increase in water pH that might accompany the institution of these changes and decrease the capacity of carbon for chloramine[23][24].

Activated carbon may be regenerated by a number of techniques, including oxidation at high temperatures and stripping with low-pressure steam or solvents. Regeneration of activated carbon, also known as reactivation, is used in industrial applications where activated carbon can be used to remove organic and inorganic substances such as pollutants from process streams. No evidence that regenerated carbon was being used for haemodialysis applications could be found. However, it was deemed prudent to prohibit the use of regenerated carbon in haemodialysis applications to avoid any potential hazard resulting from residual toxins that could remain in the carbon following regeneration.

Depending on the source material used for its manufacture, and the manufacturing process, granular activated carbon might contain carbon fines and other contaminants, such as aluminium. If present,

these substances will leach out of a carbon bed during the initial stages of operation. Carbon fines can contribute to fouling of reverse osmosis membranes downstream of the carbon beds and any metal ions can add to the burden of contaminants, which should be removed from the water. Acid washing of carbon minimizes the amount of fines and other contaminants, and a requirement for the use of acid-washed carbon was considered. No consensus could be reached on this issue because rinsing of carbon beds before they are placed online in a water treatment cascade will also effectively remove fines and other contaminants.

The requirement for two beds in series and a 10 min empty-bed-contact-time was waived for portable dialysis systems provided there is a redundant means of chloramine removal because of the impracticality of providing these features while retaining the portability of the system. Possible alternatives include a granular activated carbon bed followed by a dense carbon block and two carbon block filters in series. However, when a single carbon bed is used, it is important to ensure that the bed has adequate capacity to remove chloramine for the duration of an entire treatment given the typical feed water concentration of chloramine in the setting where the bed is being used.

Although treatment of water by carbon is the usual method of meeting the requirement of 4.1.2 when the feed water contains chloramine, in certain situations, such as acute or home dialysis with portable water treatment systems, it might not be practical to use the volume of carbon required for this purpose. In such circumstances, combining limited carbon with the addition of ascorbic acid to the acid concentrate has been used to eliminate chloramine from the final dialysis fluid[23]. A minimum contact time is required for ascorbic acid to neutralize chloramine in water. If ascorbic acid is being used to neutralize chloramine, and unexplained red blood cell destruction or anaemia occurs, the effectiveness of the ascorbic acid neutralization of chloramine should be investigated.

In most circumstances, conventional carbon systems provide months of effective chlorine/chloramine removal. Occasionally, conventional carbon systems experience premature breakthrough necessitating carbon bed replacement/exchange within days rather than months. These occasions could be episodic or persistent in nature. Episodic carbon filter breakthrough is often associated with periodic municipal water treatment practices, such as short-term substitution of free chlorine for chloramine. Persistent difficulties with premature breakthrough of carbon systems could be related to the source water itself (e.g pH, TOC level,) or a routine municipal water treatment practice, such as the addition of corrosion inhibitors. The occurrence of these problems seemed to be increasing. Therefore, clauses on optional water purification system devices that might help address recurrent premature exhaustion of carbon media or enhance the efficiency of the carbon media have been added. Two approaches were included: anion exchange resins that scavenge large organic molecules that can coat the carbon surface, and systems that inject sodium bisulphite, which reduces chloramine to chlorine, or acid to adjust the pH to the optimal range for removal of chloramine by carbon. Including the use of redox alloy media (RAM), also referred to as kinetic degradation fluxion (KDF), was also considered. This material can be an effective pretreatment for conventional carbon filters experiencing premature breakthrough due to municipal short-term substitution of free chlorine for chloramine or for supply waters having high organic loading. A disadvantage of KDF media is that both copper and zinc are eluted from the medium, albeit at very low levels. Concerns about how the eluted copper and zinc might affect downstream devices, together with questions about the effectiveness of KDF media, led to the omission of this alternative.

A.2.2.9 Chemical injection systems

There were reservations about the addition of chemicals to the water. However, it was recognized that the addition of chemicals could be necessary in some circumstances if a facility is to meet the maximum contaminant levels set forth in 4.1.2. For example, if the municipal water contains high levels of *N*-chloramines or chloramine in the presence of orthophosphate or polyphosphate, injection of sodium bisulphite could 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 feed water. At pH levels below 7, the rejection of fluoride can be substantially reduced, compared to its rejection at a pH of 8.

A.2.2.10 Reverse osmosis

A reverse osmosis system should demonstrate delivery of water meeting the requirements of 4.1.2 and 4.1.4; otherwise, additional treatment devices should be recommended to the user. Surveillance requirements for reverse osmosis systems are recommended on the basis of totally different degradation characteristics of these systems as compared with deionizer systems. On initial setup, the reverse osmosis device should have a rejection rate that ensures that the product water of the water treatment system meets the requirements of 4.1.2. Because this rejection rate varies with different installations, an absolute level is not required. Surveillance is defined in terms of the salt passage rate or percent rejection and a threshold level of product water resistivity or conductivity. Conformity with both observed parameters is required because an increase in feed water contaminants could result in product water unsuitable for haemodialysis applications even though the percent rejection of the membrane modules remains high.

Consensus could not be reached on how to establish the alarm limits for rejection and product water resistivity or conductivity. As noted above, changes in feed water quality will result in changes in product water quality even though rejection remains constant. Also, a significant change in the feed water concentration of one trace inorganic contaminant might not appreciably alter the product water resistivity even though the product water concentration of that contaminant exceeds the allowable limit. For that reason, some felt that routine analysis of feed water quality should be emphasized. Others felt that the rejection alarm limit could be set based on the reduction ratio for each contaminant that can be achieved by reverse osmosis and the assumption that the feed water meets the national requirements for drinking water, or in the case of countries without a legislative framework for such a requirement, the World Health Organization (WHO) guidelines on drinking water[25]. Either approach could be effective when incorporated into an overall surveillance programme designed to protect the patient against exposure to contaminant levels in excess of those listed in Annex B (Tables B.1 and B.2)

In respect of inclusion of a requirement that reverse osmosis systems incorporate as a means of diverting the product water to drain in the event of a product water conductivity or rejection rate alarm, consensus could not be reached except in a situation where the reverse osmosis is the final stage in the water treatment.

A direct feed water distribution system, incorporating a divert-to-drain would cause an immediate alarm condition with most single pass dialysis machines resulting from the interruption of the water supply. Although reverse osmosis membranes tend to fail gradually, there remains a risk to the patient in that the requirements outlined in Annex B (Tables B.1 and B.2) are not met. These risks are different from those associated with the exhaustion of a deionizer where very high levels of contaminants, such as fluoride, can occur abruptly in the product water. However, not withstanding that consensus could not be reached on how to establish the alarm limits for rejection and product water resistivity or conductivity, continuation of dialysis following an alarm requires a determination of the alarm cause to be identified, and the risk of continuing treatment assessed. Therefore, a divert-to-drain was included as a requirement.

Because reverse osmosis systems are often remote from the patient treatment area, a visual and/or audible alarm in the patient treatment area was considered necessary. The audible alarm, should be capable of being muted for up to 3 min (180 s) following activation was considered appropriate.

A.2.2.11 Deionization

Deionizer systems, during exhaustion, have the capability of releasing into the water potentially harmful contaminants at levels much higher than are present in the untreated feed water[26]. The monitor level of 1 MΩ·cm specific resistivity was selected as the point at which most of the useful capacity of the deionizers used in dialysis water treatment has been consumed and below which rapid degradation of ion removal efficiency takes place; 1 MΩ·cm specific resistivity is not the minimum safe value for dialysis water, but deionizer systems producing water dropping below this value are in danger, during the following dialysis treatment, of producing water high in toxic contaminants as the final deterioration of resin accelerates. A requirement that the product water be diverted to drain was included because of the acute danger that an exhausted deionizer can pose to patients[27] [28]. The requirement for activated carbon in advance of the deionizer prevents generation of possibly

carcinogenic nitrosamines[29]. Deionizers are subject to bacterial contamination because of the porous structure of the resins. Although the level of bacterial contamination in product water from deionizers varies widely, it is generally highest after the deionizer has been idle for some time and lowest after continuous use. Because deionizers are usually placed last in a purification cascade, they should be followed by an endotoxin retentive filter or another bacteria and endotoxin removing device to prevent bacterial contamination of the water storage and distribution system.

For the reasons outlined in A.2.2.10 for reverse osmosis, it was decided to retain the requirements for a visual and an audible alarm.

A.2.2.12 Endotoxin retentive filters

Endotoxin retentive filters are increasingly being used to provide water of high microbiologic quality for dialysis applications. Endotoxin retentive filters include ultrafilters that remove endotoxin primarily by size exclusion, although some can also remove some endotoxin by adsorption to the membrane material, and microfilters that remove endotoxin primarily by adsorption to the membrane material. Because of the two different mechanisms of endotoxin removal, and because the role of endotoxin retentive filters is to remove bacteria and endotoxins, they have been defined in these terms. This choice also provides a basis for observing the performance of endotoxin retentive filters after they have been installed in a water treatment purification system. Consensus could not be reached regarding minimum performance criteria for the removal of bacteria and endotoxins by an endotoxin retentive filter. One factor contributing to this impasse is the dependence of filter performance on the test conditions. Therefore, it was decided to require that manufacturers disclose the minimum performance of their device and that the device be required to perform to at least this level under stated operating conditions. Some considered that an endotoxin retentive filter should be able to reduce the concentration of bacteria in the feed water to the filter by a factor of at least 10^7 and that of endotoxin by a factor of at least 10^3. Methods for determining bacteria and endotoxin rejection by ultrafilters have been published by the Japanese Standards Institute and ASTM International[2][3][4].

The recommendation to use endotoxin retentive filters in a cross-flow configuration is aimed at preventing excessive replacement of membrane modules, which could result from rapid fouling if the filter is operated in the dead-end mode. However, a dead-end configuration might perform satisfactorily in situations where the water quality is generally good (for example, as final filtration of water immediately before its use in dialyser reprocessing equipment). Differential pressure measurements can be used to observe fouling of both cross-flow and dead-end filters.

A.2.2.13 Storage and distribution

A.2.2.13.1 Piping systems

The distribution system has been implicated in several bacterial contamination episodes involving dialysis patients[29]. Specific design criteria, such as minimum flow velocities, to minimize bacterial proliferation and biofilm formation were considered[30][31]. Desirable design criteria include use of a distribution loop, an absence of multiple branching and dead-ended pipes, the use of simple wall outlets with the shortest possible fluid path, a minimum of pipe fittings, and the use of valves with minimal dead space. 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 could serve as sites for bacterial colonization. Agreement could not be reached concerning a minimum flow velocity. Some were of the opinion that the low shear stresses existing at the internal surface of a pipe operating at flow rates that are feasible in distribution systems for dialysis water are insufficient to prevent bacterial adhesion and biofilm formation. On the other hand, data from the semiconductor industry showed that a Reynolds number of 3 000 in a piping system was sufficient to prevent bacterial contamination in water. A Reynolds number of approximately *Re* 3000 is obtained with a flow velocity of about 0,15 m/s in a 2 cm diameter pipe (0,5 ft/s in a 3/4” diameter pipe)[31]. However, even in systems operating with *Re* 3 000, biofilm can be found on the internal surface of the pipes. In many dialysis facilities, there is no flow through the distribution system when the dialysis facility is not in operation, such as at night and on Sundays. Even if it were possible to specify a minimum flow velocity that was effective in reducing

biofilm formation and bacterial contamination, use of such a minimum flow velocity would not provide a substitute for regular disinfection of the distribution system.

Direct feed systems commonly return water from the dialysis water distribution loop to the feed side of the reverse osmosis unit, before the pressurizing pump. With this configuration, it is possible for water from the feed side of the reverse osmosis unit to flow retrograde into the dialysis water distribution loop if the pressure in the distribution loop suddenly decreases as the result of a sudden increase in demand for dialysis water. Because retrograde flow allows contaminated water to enter the dialysis water distribution system, it was considered necessary to recommend some means of preventing retrograde flow. A common method is to include dual check valves at the end of the distribution loop. Some were concerned that there is no means of observing the integrity of these valves. A second approach is to return the dialysis water into a break tank at the inlet to the pressurizing pump of the reverse osmosis unit.

A.2.2.13.2 Storage tanks

When storage tanks form part of the water treatment infrastructure, the volume and low water velocities in such tanks predispose them to bacterial contamination. As a consequence, tanks should be designed with features that facilitate disinfection procedures and prevent the entry of bacteria.

A.2.2.13.3 Ultraviolet irradiators

The effectiveness of UV irradiation depends on the dose of radiant energy. Several studies have demonstrated that a dose of 30 mW s/cm^2 will kill greater than 99,99 % of a variety of bacteria, including *Pseudomonas* species, in a flow-through device[32]. However, certain gram-negative water bacteria appear to be more resistant to UV irradiation than others, and use of sub-lethal doses of UV radiation, or an insufficient contact time, could lead to proliferation of these resistant bacteria in the water system[33].

The radiant energy emitted by the mercury vapour lamps used in UV irradiators decreases with time. If the lamp is not replaced before its radiant energy decreases below the effective threshold, resistant bacteria could also develop. Therefore, the requirement for an online monitor of the radiant energy emitted by the lamp is included in this document. Because the effectiveness of UV irradiation depends on the geometry of the device and the exposure time of water to the radiation, the manufacturer of a UV irradiation device is required to provide information on the killing of specific bacteria under specified operating conditions. Because UV irradiators do not eliminate endotoxin and could even increase endotoxin concentrations by killing bacteria, a recommendation was included that they be followed by an endotoxin retentive filter. Use of an endotoxin retentive filter was not made a requirement however, because reliance on an endotoxin retentive filter to remove endotoxin should not be considered an alternative to identifying and eliminating the source of bacterial contamination.

Ultraviolet irradiation has also been used to eliminate chloramine as an alternative or adjunct to activated carbon. Ultraviolet irradiation at a wavelength of 254 nm converts chloramine (NH_2Cl) to chloride and ammonium ions, which are easily rejected by reverse osmosis. Hard water, high total dissolved solids (TDS), or high levels of fluoride, iodine, iron, or manganese could interfere with penetration of ultraviolet irradiation through the water and inhibit the effectiveness of ultraviolet irradiation in eliminating chlorine/chloramine.

A.2.2.13.4 Hot water disinfection systems

Hot water disinfection of dialysis water storage and distribution systems is one means of controlling bacterial proliferation. The manufacturer of a hot water disinfection system should validate the recommended operating conditions to demonstrate that they provide adequate reduction in bacterial levels and also disclose these operating specifications of the system. Repeated exposure to hot water might have a deleterious effect on some plastic piping. Therefore, a requirement that manufacturers of hot water disinfection systems include a warning in their product labelling about the need to use heat-resistant materials in piping systems to be disinfected with hot water was added to this document.

A.2.2.13.5 Ozone disinfection systems

Ozonation is being introduced as a new means of controlling bacterial proliferation in dialysis water storage and distribution systems. This technology might have widespread applicability in dialysis facilities in light of the increased concern about endotoxin contamination of dialysis fluid. Insufficient data are available to set performance standards for such systems, such as ozone concentration and exposure time. Therefore, a requirement that the manufacturer of an ozone disinfection system disclose the operating specifications of the system until such time as performance criteria could be established was included. The manufacturer of an ozone disinfection system should validate the recommended operating conditions to demonstrate that they provide adequate reduction in bacterial and, if applicable, endotoxin levels. The presence of ozone in dialysis water could be harmful to patients, however robust data demonstrating clinical effects is currently absent. It is, however, known that low levels of ozone have the potential to supress immune system response[34]. Therefore, a requirement for manufacturers to include a warning that product water should not be used until ozone produced in the disinfection process has dissipated [see 6.3 r)] was included. The manufacturer should validate that residual ozone in the product water falls to acceptable levels at the end of the recommended minimum elapsed time between disinfection and use of the product water. Alternatively, the manufacturer of an ozone disinfection system can provide the user with a means of verifying that the residual ozone is within acceptable limits before product water is used. Repeated exposure to ozone could have a deleterious effect on some plastic piping. Therefore, a requirement that manufacturers of ozonation systems include a warning in their product labelling about the need to use ozone-resistant materials in piping systems to be disinfected with ozone was added to this document.

A.2.2.13.6 Sodium hypochlorite disinfection

Removal of free chlorine to a maximum level of 0,5 mg/l and combined chlorine/chloramines to a maximum level of 0,1 mg/l is necessary to protect the hemodialysis patient from hemolytic reactions (hemolysis, hemolytic anemia, and methemoglobinemia) and, EPO resistance[35][36][37][38]. Chlorine can be present in water as both free chlorine and chlorine in chemically combined forms such as chloramine. Determining the level of chloramine typically involves measuring both total chlorine and free chlorine and assigning the difference in concentrations to chloramine. During the second revision of this document in 2008, the working group chose to simplify this situation by setting a maximum allowable level for total chlorine at the same value used previously for chloramine (0,1 mg/l), thus permitting a single test to be used. It should be noted that total chlorine is defined as the sum of free chlorine and combined chlorine.

If sodium hypochlorite (bleach) is used for cleaning or disinfecting the internal pathways of dialysis equipment, including but not limited to water treatment loops, concentrate containers, mixers, and delivery systems, the post rinse water residual level of free chlorine shall be as specified by the manufacturer's instructions.

A.3 Testing

A.3.1 Conformity with dialysis water quality requirements — Microbiology of dialysis water

The rationale for the culturing methods required in this document is set forth in ISO 23500-3:2019, Annex A.3.

A.3.2 Conformity with water treatment equipment requirements — Materials compatibility

It has been argued that the biocompatibility tests outlined in the appropriate *pharmacopeia* were not useful for water treatment equipment because they were not sensitive enough to detect the presence of small amounts of toxin in large volumes of water. It was proposed that the appropriate *pharmacopeia* biocompatibility tests be replaced by leach testing and measurement of total organic carbon in the leachate. After discussion, this proposal was rejected because there was no clinical outcomes data