



BSI Standards Publication

Preparation and quality management of fluids for haemodialysis and related therapies

Part 1: General requirements

National foreword

This British Standard is the UK implementation of EN ISO 23500-1:2024. It is identical to ISO 23500-1:2024. It supersedes BS EN ISO 23500-1:2019, which is withdrawn.

The UK participation in its preparation was entrusted to Technical Committee CH/150/2, Cardiovascular implants.

A list of organizations represented on this committee can be obtained on request to its committee manager.

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English Version

Preparation and quality management of fluids for
haemodialysis and related therapies - Part 1: General
requirements (ISO 23500-1:2024)

Préparation et management de la qualité des liquides
d'hémodialyse et de thérapies annexes - Partie 1:
Exigences générales (ISO 23500-1:2024)

Herstellung und Qualitätsmanagement von
Flüssigkeiten für die Hämodialyse und verwandte
Therapien - Teil 1: Allgemeine Anforderungen (ISO
23500-1:2024)

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COMITÉ EUROPÉEN DE NORMALISATION
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European foreword

This document (EN ISO 23500-1:2024) has been prepared by Technical Committee ISO/TC 150 "Implants for surgery" in collaboration with Technical Committee CEN/TC 205 "Non-active medical devices" the secretariat of which is held by DIN.

This European Standard shall be given the status of a national standard, either by publication of an identical text or by endorsement, at the latest by March 2025, and conflicting national standards shall be withdrawn at the latest by March 2025.

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

This document supersedes EN ISO 23500-1:2019.

Any feedback and questions on this document should be directed to the users' national standards body/national committee. A complete listing of these bodies can be found on the CEN website.

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Endorsement notice

The text of ISO 23500-1:2024 has been approved by CEN as EN ISO 23500-1:2024 without any modification.

Contents

Page

Foreword	v
Introduction	vii
1 Scope	1
2 Normative references	1
3 Terms and definitions	2
4 Quality requirements	9
4.1 General	9
4.2 Dialysis water	10
4.2.1 General	10
4.2.2 Chemical contaminants in dialysis water	10
4.2.3 Organic carbon, pesticides and other chemicals	12
4.2.4 Microbiological contaminants in dialysis water	12
4.3 Requirements for concentrate	12
4.3.1 Chemical and microbiological contaminants in concentrate	12
4.3.2 Water used to prepare concentrate	13
4.4 Requirements for dialysis fluid	13
4.4.1 General	13
4.4.2 Microbiological requirements for standard dialysis fluid	13
4.4.3 Microbiological requirements for ultrapure dialysis fluid	13
4.4.4 Microbiological requirements for online-prepared substitution fluid	14
4.5 Record retention	14
5 System design and technical considerations	14
5.1 General	14
5.2 Technical aspects	15
5.3 Microbiological aspects	16
5.4 Environmental impact	16
6 Validation of system performance	16
6.1 General	16
6.2 Validation plan	18
6.3 Installation and operational qualification	18
6.4 Performance qualification	18
6.5 Validation	19
6.5.1 General	19
6.5.2 Initial validation	19
6.5.3 Retrospective (annual) validation	19
6.5.4 Revalidation	19
6.6 Monitoring and surveillance	20
7 Quality management	20
7.1 General	20
7.2 Surveillance of fluid quality	21
7.2.1 Surveillance of dialysis water quality	21
7.2.2 Surveillance of concentrate quality	21
7.2.3 Surveillance of dialysis fluid quality	21
7.3 Surveillance of water treatment equipment	21
7.3.1 General	21
7.3.2 Surveillance of sediment filters	21
7.3.3 Surveillance of cartridge filters	22
7.3.4 Surveillance of softeners	22
7.3.5 Surveillance of carbon media	23
7.3.6 Surveillance of chemical injection systems	23
7.3.7 Surveillance of reverse osmosis	24
7.3.8 Surveillance of deionization	25

7.3.9	Surveillance of bacteria and endotoxin-retentive filters	25
7.3.10	Surveillance of dialysis water storage and distribution	25
7.3.11	Surveillance of bacterial control devices	26
7.4	Surveillance of concentrate preparation	27
7.4.1	Surveillance of mixing systems	27
7.4.2	Surveillance of additives	27
7.5	Surveillance of concentrate distribution	27
7.6	Surveillance of dialysis fluid proportioning	27
8	Strategies for microbiological control	28
8.1	General	28
8.2	Disinfection	28
8.2.1	General	28
8.2.2	Microbiological aspects of fluid system design	28
8.2.3	Disinfection frequency	29
8.3	Microbiological surveillance methods	30
8.3.1	General	30
8.3.2	Sample collection	31
8.3.3	Heterotrophic plate count	32
8.3.4	Bacterial endotoxin test	34
8.3.5	Determination of yeast and mould	34
9	Location of and access to the water treatment system	35
10	Personnel	35
Annex A (informative) Rationale for the development and provisions of this document		36
Annex B (informative) Equipment		42
Annex C (informative) Surveillance guidelines for water treatment equipment, distribution systems and dialysis fluid		61
Annex D (informative) Strategies for microbiological control		65
Annex E (informative) Validation		75
Annex F (informative) Special considerations for home haemodialysis		83
Annex G (informative) Special considerations for acute haemodialysis		90
Annex H (informative) Further considerations for different water quality monitoring approaches		95
Annex I (informative) Additional considerations for risk assessment		97
Bibliography		100

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 document should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

ISO draws attention to the possibility that the implementation of this document may involve the use of (a) patent(s). ISO takes no position concerning the evidence, validity or applicability of any claimed patent rights in respect thereof. As of the date of publication of this document, ISO had not received notice of (a) patent(s) which may be required to implement this document. However, implementers are cautioned that this may not represent the latest information, which may be obtained from the patent database available at www.iso.org/patents. ISO shall not be held responsible for identifying any or all such patent rights.

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

This document was prepared by Technical Committee ISO/TC 150, *Implants for surgery*, Subcommittee SC 2, *Cardiovascular implants and extracorporeal systems*, in collaboration with the European Committee for Standardization (CEN) Technical Committee CEN/TC 205, *Non-active medical devices*, in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

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

The main changes are as follows:

- WHO Drinking Water Guideline has been used as the main drinking water quality reference instead of the US EPA or other European standards;
- thallium has been removed from the list of contaminants, as no studies have reported data to indicate that this contaminant is of particular concern in the haemodialysis setting;
- alternative water treatment technologies (e.g. reverse osmosis pre-treatment with ultrafiltration) have been included in the subclauses dealing with water treatment technology (refer to [B.2.7](#) and [B.2.8](#));
- a new annex ([Annex H](#)) has been added to provide clarification of the different water quality monitoring approaches (online versus offline monitoring);
- the microbiological analytic methods have been updated to include endotoxin testing using recombinant Factor C (rFC), flow cytometry, autofluorescence and rapid tests (e.g. ATP);
- a new annex ([Annex I](#)) has been added to provide guidance on risk assessment;
- the validation of water treatment systems has been revised to include validation steps (e.g. installation qualification, operational qualification, performance qualification and revalidation);
- further guidance has been added on technical needs after the typical technical interventions in [Clause E.4](#).

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

ISO 23500-1:2024(en)

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

Introduction

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

The objective of the ISO 23500 series is to provide users with guidance for handling water and concentrates and for the production and quality oversight of dialysis fluid used for haemodialysis. The need for such guidance is based on the critical role of dialysis fluid quality in providing safe and effective haemodialysis, and the recognition that day-to-day dialysis fluid quality is under the control of the healthcare professionals who deliver dialysis therapy.

[Annex A](#) provides further information on the rationale for the development and provisions of this document.

The equipment used in the various stages of dialysis fluid preparation is generally obtained from specialized vendors. Dialysis practitioners are generally responsible for maintaining that equipment following its installation. Therefore, this document provides guidance on quality oversight and maintenance of the equipment to ensure that dialysis fluid quality is acceptable at all times. At various places in this document, the user is advised to follow the manufacturer's instructions regarding the operation and maintenance of equipment. In instances in which the equipment is not obtained from a specialized vendor, it is the responsibility of the user to validate the performance of the equipment in the haemodialysis setting and to ensure that appropriate operating and maintenance manuals are available.

[Annex B](#) provides further information on the system components that are used for water treatment, concentrate and dialysis fluid preparation at a dialysis facility. These descriptions are intended to provide the user with a basis for understanding why certain equipment can be required and how it should be configured; the descriptions are not intended to be detailed design standards. Requirements for water treatment equipment are provided in ISO 23500-2.

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

This document reflects the conscientious efforts of healthcare professionals, patients and medical device manufacturers to develop recommendations for handling water and concentrates and for the production and surveillance of dialysis fluid for haemodialysis and protecting haemodialysis patients from adverse effects arising from known chemical and microbial contaminants that can be found in improperly prepared dialysis fluid.

[Annexes F](#) and [G](#) provide further information regarding the special considerations for home and acute haemodialysis. This document together with its constituent parts is directed towards the healthcare professionals involved in the management or routine care of haemodialysis patients and responsible for the quality of dialysis fluid. However, the physician in charge of dialysis has the ultimate responsibility for ensuring that the dialysis fluid is correctly formulated and meets the requirements of all applicable quality standards.

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

Part 1: General requirements

1 Scope

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

This document is applicable to

- the quality management of equipment used to treat and distribute water used for the preparation of dialysis fluid and substitution fluid, from the point at which municipal water enters the dialysis facility to the point at which the final dialysis fluid enters the dialyser or the point at which substitution fluid is infused.
- the quality management of the equipment used to prepare acid and bicarbonate concentrate from powdered or other highly concentrated media at a dialysis facility, and
- the preparation of the final dialysis fluid or substitution fluid from dialysis water and concentrates.

This document does not apply to

- sorbent-based dialysis fluid regeneration systems that regenerate and recirculate small volumes of dialysis fluid,
- systems for continuous renal replacement therapy that use pre-packaged solutions, and
- systems and solutions for peritoneal dialysis.

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

2 Normative references

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

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

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

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

3 Terms and definitions

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

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

- ISO Online browsing platform: available at <https://www.iso.org/obp>
- IEC Electropedia: available at <https://www.electropedia.org/>

3.1

acetate concentrate

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

Note 1 to entry: Acetate concentrate can contain glucose.

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

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

3.2

acid concentrate

A-concentrate

low pH mixture of salts that, when diluted with *dialysis water* (3.17) and *bicarbonate concentrate* (3.6), yields *dialysis fluid* (3.15) for use in dialysis

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

Note 2 to entry: Acid concentrate can contain glucose.

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

3.3

action level

value from monitoring that necessitates immediate intervention

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

3.4

additive

spike

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

3.5

bacteria and endotoxin-retentive filter

BERF

endotoxin retentive filter

ERTF

membrane filter used to remove *endotoxins* (3.20) and microorganisms from *dialysis water* (3.17) or *dialysis fluid* (3.15)

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

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

3.6**bicarbonate concentrate**

B-concentrate

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

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

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

Note 3 to entry: Dry sodium bicarbonate, without added sodium chloride, is also used in concentrate generators to produce a concentrated solution of sodium bicarbonate used by the dialysis machine to make dialysis fluid.

3.7**biofilm**

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

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

Note 2 to entry: A certain amount of biofilm formation is considered unavoidable in *dialysis water* (3.17) systems. When the level of biofilm is such that the *action levels* (3.3) for microorganisms and *endotoxins* (3.20) in the dialysis water are routinely reached or exceeded, the operation of the system is compromised from a medical and technical point of view. This level of biofilm formation is often referred to as biofouling.

3.8**bulk delivery**

delivery of large containers of concentrate to a dialysis facility

Note 1 to entry: Bulk delivery can be containers such as drums, which can be pumped into a *storage tank* (3.41) maintained at the *user's* (3.44) facility. Alternatively, the drums can be left at the facility and used to fill transfer containers to transfer the concentrate to the dialysis machines. Bulk delivery can also include large containers for direct connection to a central concentrate supply system.

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

3.9**central concentrate system**

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

3.10**central dialysis fluid delivery system**

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

3.11**combined chlorine**

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

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

3.12**free chlorine**

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

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

3.13

total chlorine

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

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

3.14

colony-forming unit

CFU

aggregation of microorganisms arising from a single cell or multiple cells

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

3.15

dialysis fluid

DEPRECATED: dialysate

DEPRECATED: dialysis solution

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

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

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

Note 3 to entry: Dialysis fluid does not include pre-packaged parenteral fluids used in some renal replacement therapies, such as haemodiafiltration and *haemofiltration* (3.25).

3.16

dialysis fluid delivery system

device that

- prepares *dialysis fluid* (3.15) online from *dialysis water* (3.17) and concentrates, or stores and distributes premixed dialysis fluid,
- circulates the dialysis fluid through the dialyser,
- monitors the dialysis fluid for temperature, conductivity (or equivalent), pressure, flow and blood leaks, and
- prevents dialysis during *disinfection* (3.18) or cleaning modes

Note 1 to entry: The term includes reservoirs, conduits, proportioning devices for the dialysis fluid and monitors and associated alarms and controls assembled as dialysis fluid delivery systems.

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

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

3.17

dialysis water

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

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

3.18

disinfection

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

3.19

empty-bed contact time

EBCT

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

Note 1 to entry: EBCT is used as an indirect measure of how much contact occurs between particles, such as activated carbon, and water as the water flows through a bed of particles.

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

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

where

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

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

3.20

endotoxin

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

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

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

3.21

endotoxin unit

EU

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

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

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

3.22

germicide

agent that kills microorganisms

3.23

haemodiafiltration

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

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

3.24**haemodialysis**

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

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

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

3.25**haemofiltration**

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

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

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

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

3.26**heterotrophic**

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

3.27**initial validation**

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

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

3.28***Limulus* amoebocyte lysate test****LAL test**

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

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

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

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

3.29**manufacturer**

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

Note 1 to entry: Manufacturer includes, but is not limited to, those who perform the functions of contract sterilization, installation, relabelling, remanufacturing, repacking or specification development and initial distributions of foreign entities performing these functions.

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

3.30

microbial contamination

presence of unintended bacteria, fungi, protozoa or viruses

[SOURCE: ISO 11139:2018, 3.171]

3.31

non-pyrogenic

not pyrogenic

not eliciting a *pyrogen* (3.35) reaction

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

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

3.32

operational qualification

OQ

verification (3.46) of the correct operation of the system and comparison of the system performance with the systems functional performance

3.33

product water

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

3.34

proportioning system

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

3.35

pyrogen

fever-producing substance

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

3.36

retrospective validation

annual *validation* (3.45) for a system

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

- modification of the maintenance and surveillance plans (includes performance qualification as applicable);
- modification to the system (includes *initial validation* (3.27), operational qualification and performance qualification);
- changes in the requirements for *dialysis fluid* (3.15) quality;
- changes in the feed water quality outside the acceptable limits previously foreseen.

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

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

3.37

revalidation

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

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

3.38

sodium hypochlorite

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

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

3.39

source water

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

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

3.40

sterile

free from viable microorganisms

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

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

3.41

storage tank

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

3.42

substitution fluid

substitution solution

replacement solution

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

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

3.43

total dissolved solids

TDS

sum of all ions in a solution, often approximated by means of electrical conductivity or resistivity measurements

Note 1 to entry: TDS measurements are commonly used to evaluate the performance of reverse osmosis units. TDS values are expressed in milligrams per litre (mg/l), in terms of

- CaCO_3 ,
- NaCl,
- KCl, or
- TDS 442 equivalents [TDS 442 is a solution of sodium sulfate (40 %), sodium bicarbonate (40 %), and sodium chloride (20 %) that closely represents the conductivity to concentration relationship, for natural freshwater].

3.44

user

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

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

3.45

validation

process of documenting that the *dialysis water* (3.17) treatment and *dialysis fluid* (3.15) production systems, when installed and operated according to the *manufacturer's* (3.29) recommendations, consistently produces dialysis water or dialysis fluid meeting the stipulated quality levels

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

Note 2 to entry: Different types of validation exist e.g. *Initial validation* (3.27), *retrospective (annual) validation* (3.36) and *revalidation* (3.37).

3.46

verification

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

3.47

water supply

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

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

3.48

water treatment system

collection of water treatment devices and associated piping, pumps, valves, gauges, etc., that together produce water for dialysis meeting the requirements of ISO 23500-3 for *haemodialysis* (3.24) applications and deliver it to the point of use

4 Quality requirements

4.1 General

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

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

4.2 Dialysis water

4.2.1 General

The requirements contained in [4.2](#) apply to dialysis water at its point of use. As such, these requirements apply to the water treatment system as a whole and not to each of the devices that make up the system. However, collectively, the individual devices shall produce water that, at a minimum, meets the requirements of [4.2](#).

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

4.2.2 Chemical contaminants in dialysis water

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

The manufacturer or supplier of a complete water treatment system should recommend a system that is capable of meeting these requirements based on a feed water analysis.

Conformity shall be shown by:

- using analytical methods referenced in ISO 23500-3 or other appropriately validated and comparable analytical methods, or
- when analytical methodology for the individual trace elements listed in [Table 2](#) is not available and the water can be demonstrated to meet the standards for potable water as defined by the WHO,^[18] an analysis for total heavy metals with a maximum allowable level of 0,1 mg/l may be used, or
- if neither of the above options are available, conformity with the requirements of [Table 2](#) can be met by using water that can be demonstrated to meet the potable water requirements of the WHO and a reverse osmosis system with a rejection of >90 % based on conductivity, resistivity or TDS.

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

The system design should reflect possible seasonal variations in feed water quality. The manufacturer or supplier of a complete water treatment and distribution system should demonstrate that the complete water treatment, storage and distribution system is capable of meeting the requirements of ISO 23500-3 at the time of installation.

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

Table 1 — Maximum allowable levels of toxic chemicals and dialysis fluid electrolytes in dialysis water^{a,b}

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

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

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

^c Unless otherwise noted.

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

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

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

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

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

Contaminant	Maximum concentration mg/l
Antimony	0,006
Arsenic	0,005
Barium	0,1
Beryllium	0,000 4
Cadmium	0,001
Chromium	0,014
Mercury	0,000 2
Selenium	0,09
Silver	0,005

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

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

4.2.3 Organic carbon, pesticides and other chemicals

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

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

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

4.2.4 Microbiological contaminants in dialysis water

The total viable microbial count (TMVC) and endotoxin concentration in dialysis water shall comply with the maximum allowable levels specified [Table 3](#). Action levels for the total viable microbial count and endotoxin concentration shall also be set, based on the knowledge of the microbial dynamics of the system. Typically, the action level is set at 50 % of the maximum allowable level for bacteria and endotoxins. If a total viable microbial count or endotoxin concentration at or above the action level is observed in the dialysis water, corrective measures should be taken promptly to reduce the level. The manufacturer or supplier of a complete water treatment and distribution system should demonstrate that the complete water treatment, storage and distribution system is capable of meeting the requirements of ISO 23500-3 at the time of installation.

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

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

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

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

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

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

4.3 Requirements for concentrate

4.3.1 Chemical and microbiological contaminants in concentrate

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

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

4.3.2 Water used to prepare concentrate

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

4.4 Requirements for dialysis fluid

4.4.1 General

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

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

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

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

4.4.2 Microbiological requirements for standard dialysis fluid

The total viable microbial count and endotoxin concentration in standard dialysis fluid shall comply with the maximum allowable levels specified in ISO 23500-5 and reproduced in [Table 4](#). Action levels for the total viable microbial count and endotoxin concentration shall also be set, based on the knowledge of the microbial dynamics of the system as specified in ISO 23500-5. Typically, the action level is set at 50 % of the maximum allowable level for total viable microbial count and endotoxins. If the total viable microbial counts or endotoxin concentrations at or above the action levels are observed in the dialysis fluid, corrective measures, such as disinfection and retesting, should promptly be taken to reduce the levels.

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

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

Contaminant	Standard dialysis fluid		Ultrapure dialysis fluid
	Maximum allowable level	Action level ^b	Maximum allowable level
TMVC	<100 CFU/ml	50 CFU/ml	<0,1 CFU/ml
Endotoxin	<0,5 EU/ml	0,25 EU/ml	<0,03 EU/ml
^a The reader is cautioned to refer to the latest edition of ISO 23500-5 to ensure that there have been no changes to this table.			
^b Typically set at 50 % of the maximum allowable level. Other values can be set.			

4.4.3 Microbiological requirements for ultrapure dialysis fluid

The total viable microbial count and endotoxin concentration in ultrapure dialysis fluid shall comply with the maximum allowable levels specified in ISO 23500-5 and reproduced in [Table 4](#). If those limits are exceeded in ultrapure dialysis fluid, corrective measures should be taken to reduce the levels into an acceptable range. The user is responsible for surveillance of the dialysis fluid bacteriology of the total system following installation.

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

4.4.4 Microbiological requirements for online-prepared substitution fluid

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

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

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

The user shall follow the manufacturer's instructions for the installation, use, maintenance and conformity of the validated system. The function of the validated system shall be verified in accordance with the manufacturer's instructions at the time of installation and confirmed by the user with regular surveillance. Surveillance shall include confirmation that the dialysis water and concentrates used by the validated system to prepare the substitution fluid continue to meet the specifications of ISO 23500-4 and ISO 23500-3.

4.5 Record retention

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

5 System design and technical considerations

5.1 General

The preparation of dialysis fluid, from inlet municipal water and acquisition of concentrates to discharge of spent dialysis fluid into the drain system, involves numerous components that, together, form a dialysis fluid handling system.

The technical features of the water treatment component of that system should be based on the criteria listed in ISO 23500-2, with special regard to the aspects related to the dialysis water quality, disinfection and maintenance. Reference to specialist guidance on the design and operation of building and engineering technology applicable to healthcare delivery should be made.

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

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

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

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

5.2 Technical aspects

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

- a) The choice of the water treatment system should consider the following aspects concerning the feed water supply:
 - 1) the full chemical analysis of the feed water and silt density index (SDI);
 - 2) the microbiological load which can require the introduction of an additional chlorination step;
 - 3) the flow rates, pressure and temperature;
 - 4) the treatment techniques used by the provider of the feed water (e.g. addition of chloramine, fluoride, aluminium sulfate or other chemicals); because treatment techniques can change, ongoing communication with the provider of the feed water is recommended.

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

- b) If heat disinfection is planned for the system, the distribution loop is sanitized along with the links from the distribution loop to the dialysis machines. The demand for water during such disinfection is higher than required by the dialysis machines during operation.
- c) Commonly, reverse osmosis systems capacity is rated at a specified incoming water temperature. There should be awareness that, during the winter months, a failure to attain the specified temperature will lead to a reduced system efficiency. In order to meet the required water demand, pre-heating of the feed water or the installation of a system with increased capacity to compensate for the reduction in reverse osmosis efficiency during the winter months can be required.
- d) Disinfection of the system is the only effective method of diminishing and inactivating microflora. First and foremost, the frequency of disinfection is important. Disinfection should be performed on a regular basis to limit biofouling within the fluid pathways of the system. Second, all surfaces in the circuit should be included in the disinfection procedure. This includes the reverse osmosis membranes (especially the clean side), the distribution piping, the inlet lines to the dialysis machines (located before the disinfection circuit of the dialysis machine) and the dialysis machines (which have their own disinfection circuit and programme). Third, the disinfection procedure, when applied with a given frequency and with inclusion of all critical areas, should be capable of minimizing the effects of biofouling.

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

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

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

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

- e) Provision for adequate process surveillance should be made.

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

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

5.3 Microbiological aspects

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

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

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

- the distribution loop should be of the minimum length, and should avoid multiple branches and dead ends;
- materials shall be compatible with the different operational conditions (i.e. supply, disinfection, cleaning);
- there should be no release of chemicals and nutrients for microorganisms;
- temperature increases or exposure to sunlight should be minimized.

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

5.4 Environmental impact

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

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

6 Validation of system performance

6.1 General

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

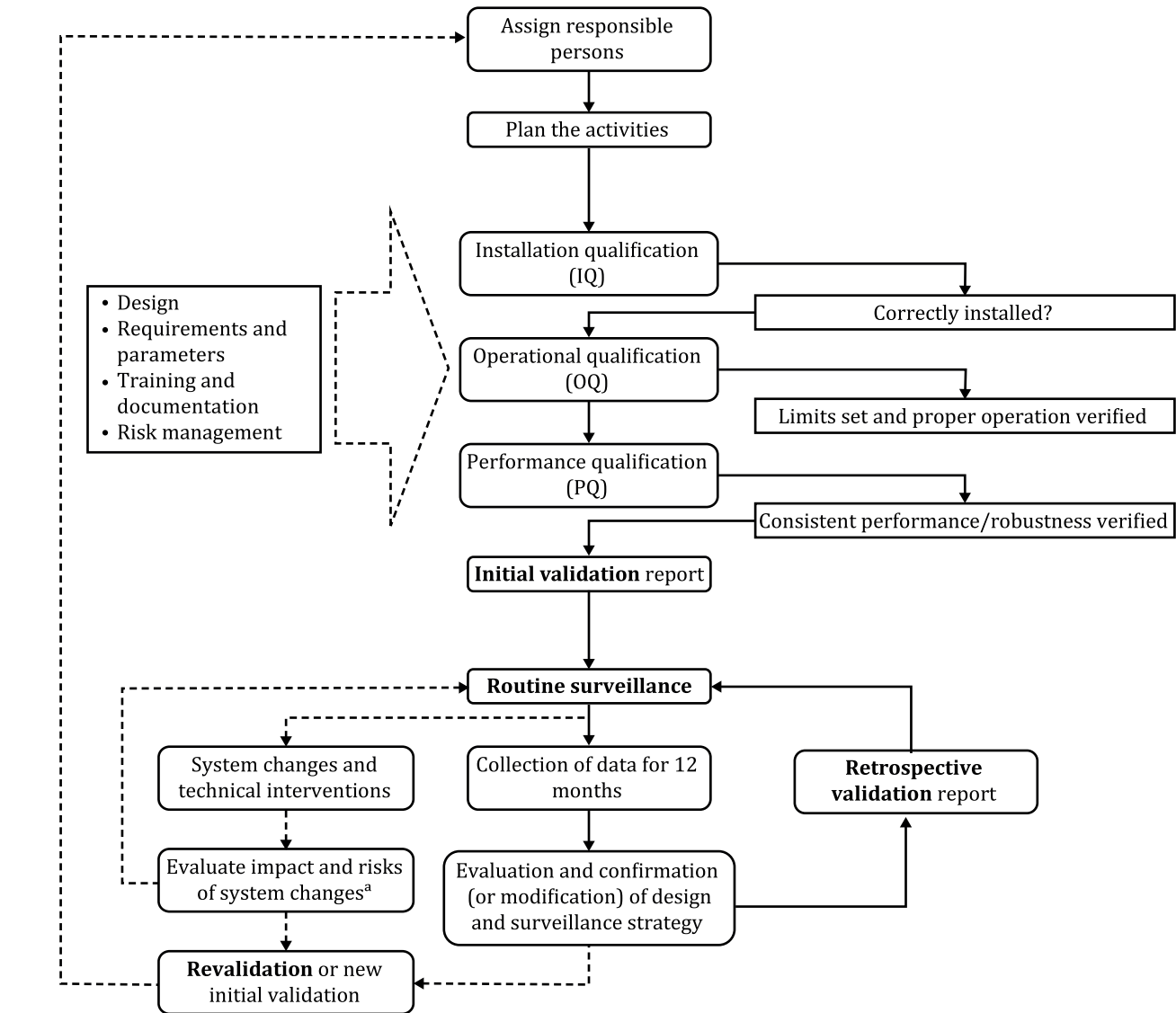
The validation process consists of the following:

- assignment of operational responsibility;
- assignment of clinical responsibility;

- assignment of legal responsibility;
- validation plan;
- installation and operational qualification;
- performance qualification;
- revalidation as it relates to routine surveillance.

[Annex E](#) provides further information on the validation process.

An example of the validation process for a fluid preparation and distribution system is presented in [Figure 1](#).



Key

- indispensable validation process steps
- - -→ other validation process steps

^a [Table E.2](#) can be used as a guide.

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

6.2 Validation plan

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

- a description of the relevant systems, equipment or processes;
- the current status of those systems, equipment or processes;
- the procedures for making changes to systems, equipment or processes;
- planning and scheduling, including the addition of new systems, activities driven by change and periodic review.

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

6.3 Installation and operational qualification

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

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

- test records;
- set-up record;
- calibration schedule;
- sampling procedures;
- maintenance (e.g. disinfection, filter changes) and surveillance (e.g. conductivity, microbiological analysis) plans;
- record of operator(s) training.

6.4 Performance qualification

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

- test records;
- chemical and microbial analyses;
- key performance indicators (e.g. pre-treatment efficiency, RO recovery/rejection rate);
- the (initial) trend analysis.

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

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

Risk influencing factors can be related to:

- type, application and frequency of disinfection;
- integration of supply lines to dialysis machines;
- material and age of the dialysis water system;
- microbiological quality of the previous installation;
- risk of suspending a dialysis session or prescription changes (e.g. dialysis technique);
- filter technology [e.g. dialysis machines fitted with bacteria and endotoxin retentive filters (BERFs)].

6.5 Validation

6.5.1 General

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

6.5.2 Initial validation

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

6.5.3 Retrospective (annual) validation

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

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

6.5.4 Revalidation

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

- any modification of the maintenance and surveillance plans (includes PQ as applicable),
- any modification of the system,
- changes in the requirements for dialysis fluid quality,
- changes in the feed water quality outside the accepted limits,
- changes to the disinfection frequency, and

— changes to the sampling frequency.

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

6.6 Monitoring and surveillance

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

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

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

Fluid sampling for microbiological monitoring and surveillance should be performed before disinfection or no sooner than 24 h after disinfection (to avoid false negative results). When disinfection is performed on consecutive days, or more frequently, samples should be taken before, and as close as practicable, to a disinfection procedure. Samples for routinely scheduled microbiology surveillance should be obtained in the shortest possible time before the scheduled disinfection.

7 Quality management

7.1 General

Quality control and quality assurance procedures should be established to ensure ongoing conformance to policies and procedures regarding fluid quality. [Clause 7](#) defines some of the surveillance activities to be performed at the dialysis facility as part of the quality assurance process. The microbiological surveillance methods described in [8.3](#) and [Table 4](#) are intended to provide examples of acceptable methods. Other test methods, provided that they have been appropriately validated and are comparable to the methods cited in [8.3](#) and [Table 4](#) can also be used. The frequency of monitoring or surveillance is generally recommended by the equipment manufacturer or by local organizations that oversee dialysis facilities. In the absence of a manufacturer's recommendations, guidance on tests to include in a quality assurance programme can be found in [Annex C](#). This guidance can also be used to supplement the manufacturer's recommendations.

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

7.2 Surveillance of fluid quality

7.2.1 Surveillance of dialysis water quality

Dialysis water quality shall be monitored on a regular basis for the chemical and microbiological contaminants listed in [4.2.2](#) and [4.2.4](#). The surveillance schedule shall be based on the results of the system validation. For an established water treatment system operating under stable conditions, chemical contaminants in dialysis water should be monitored at least annually. The exception is for total chlorine, which should be monitored as described in [7.3.5](#).

Methods for the surveillance of chemical and microbiological contaminants in dialysis water are given in ISO 23500-3.

For water treatment and distribution systems that are integrated into a single system and that have been validated to produce water meeting the quality requirements of ISO 23500-3, the manufacturer's recommendations for surveillance may be followed for the manufacturer's recommended maximum period of use according to the instructions for use, provided that the system is operated under the validated conditions.

7.2.2 Surveillance of concentrate quality

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

7.2.3 Surveillance of dialysis fluid quality

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

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

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

As dialysis fluid is prepared from dialysis water and concentrates meeting the quality requirements of ISO 23500-3 and ISO 23500-4, respectively, and since the dialysis water distribution system and dialysis fluid delivery system are required to be constructed of materials that do not contribute chemical contaminants to the water, routine surveillance of chemical contaminants in the dialysis fluid is not required.

7.3 Surveillance of water treatment equipment

7.3.1 General

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

7.3.2 Surveillance of sediment filters

There is no easy test to determine the effectiveness of a sediment filter; however, the pressure drop (ΔP) across the filter can be used to determine when the filter is retaining particulate matter to the point that the filter will no longer allow the required water flow without an excessive reduction in pressure at the outlet of the filter. A backwash cycle is used as a preventive measure to remove particulate matter from the

sediment filter and to avoid the development of an excessive pressure drop. The frequency of backwashing should follow the manufacturer's recommendations. Sediment filter surveillance should include verification that the timer used to initiate backwashing cycles is set to the correct time of day. A log sheet should be developed to record the pressure drop measurements and timer verifications.

7.3.3 Surveillance of cartridge filters

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

7.3.4 Surveillance of softeners

Softener surveillance consists of

- testing softened water for residual hardness,
- checking that the brine tank contains a sufficient supply of undissolved sodium chloride for automatically regenerating softeners, and
- checking that the timer indicates the correct time of day for time-controlled softeners.

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

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

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

The softener brine tank should be monitored on a regular basis to ensure that enough salt is present in the brine tank to form a saturated salt solution of sufficient volume for a minimum of one regeneration cycle. Salt used for regeneration should meet the specifications of the softener manufacturer. In particular, salt designated as rock salt should not be used for softener regeneration since it is not refined and typically contains sediments and other impurities that can damage O-rings and pistons, and since it can clog orifices in the softener control head. The frequency of surveillance should be based on the length of the duty cycle (see [Table C.1](#)).

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

Water hardness test results and verification of timer settings and the assessment of sufficient quantity of salt pellets according to manufacturer's instructions should be recorded in a water softener log.

7.3.5 Surveillance of carbon media

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

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

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

If chlorine is used in the water entering the water treatment system (feed water), the performance of carbon beds is monitored by measuring the total chlorine concentration in the water exiting the carbon bed or exiting the first carbon bed when a series-connected pair of beds is used. The total chlorine level shall not exceed 0,1 mg/l. If the total chlorine level of water entering the water treatment system is below the permitted limit for treated water, additional measurements in the treated water are not necessary.

Testing for total chlorine should be performed at the time that the sample is drawn by appropriately trained personnel. Total chlorine measurement can be accomplished using the N,N-diethyl-p-phenylenediamine (DPD)-based test kits, dip-and-read test strips based on Michler's thioketone (MTK or TMK), or other methods where comparable sensitivity and specificity can be demonstrated. Online monitors can also be used to measure total chlorine concentrations. If an online monitor is used, it should be used and maintained according to the manufacturer's instructions. Whichever test system is used, it should have sufficient sensitivity and specificity to resolve the maximum levels described in [4.2.2](#) (see [Table 1](#)).

When offline tests are used, testing for total chlorine should be performed at the beginning of each treatment day prior to the patient's initiating treatment. Where chloramine is used to disinfect the potable water supply at a level of 1 mg/l or more, testing should be repeated prior to the beginning of each patient shift; if there are no set patient shifts, testing should be performed approximately every 4 h during operation. More frequent surveillance can be appropriate during temporary operation with a single carbon bed which can occur following breakthrough of the first bed. In such instances, testing is performed on water exiting the second carbon bed in a series-connected pair. The decision to change the frequency of surveillance should be based on the past performance of the system and on whether changes in feed-water quality have occurred.

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

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

7.3.6 Surveillance of chemical injection systems

Systems for chemical injection should be monitored according to the manufacturer's instructions. If a facility designs its own chemical injection system, procedures should be developed to ensure proper preparation of the chemical, adequate mixing of the injected chemical with water flowing through the pre-treatment cascade, and reduction to a safe concentration level of any chemical residuals before the point of water use. The facility should also verify that the injected chemical does not degrade the performance of downstream devices, such as the reverse osmosis system. Verification can be accomplished by testing samples from the chemical reservoir and the water line after the point of injection for at least three batches of chemical.

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

verification that they meet all applicable criteria should be recorded and signed by the trained personnel performing the tests.

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

7.3.7 Surveillance of reverse osmosis

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

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

where

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

σ_P is the permeate conductivity, in S/m.

Many reverse osmosis systems have a direct reading for percent rejection.

The permeate conductivity and rejection are both affected by a number of factors, such as the salinity and composition of the feed water, the water temperature, the level of dissolved gases and the pressure in the system. Therefore, neither of them should be regarded as a true indicator of the water's suitability for dialysis. No limits are therefore set for these parameters in ISO 23500-3. Instead, they should be used to monitor changes in performance over time rather than an absolute measure of the quality. This can only be established by performing a chemical analysis of the product water according to ISO 23500-3.

NOTE 1 For two-stage reverse osmosis systems, the percent rejection of the second stage will be lower than that of the first stage because of physico-chemical phenomena.

Other parameters that should be measured include product and reject stream flow rates, and various internal pressures to the extent permitted by the system's instrumentation. Although these parameters are not directly indicative of the treated water's quality, surveillance of them can help ensure that the system is operating within the manufacturer's specifications and, thus, aids in maintaining the performance of the reverse osmosis membranes. Flow rates can be used to calculate the recovery percentage of the reverse osmosis system, r , as shown in [Formula \(2\)](#):

$$r = \frac{q_{vP}}{q_{vP} + q_{vR}} \times 100 \quad (2)$$

where

q_{vP} is the permeate volumetric flow rate;

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

NOTE 2 The percent recovery is also known as the water conversion factor. The terms are equivalent if none of the reject water stream is recycled to the feed water stream (see [B.2.8](#)). If some of the reject water stream is recycled, [Formula \(2\)](#) provides a measure of overall water utilization by the reverse osmosis system, rather than the recovery of water during a single pass through the membrane module.

NOTE 3 The permeate water flow rate varies with operating pressure and temperature. To enable comparisons to be made under different operating conditions, a normalized permeate flow rate can be calculated. Methods for calculating the normalized permeate flow rate are available from reverse osmosis membrane manufacturers or can be found in ASTM D4516-19a (2019)^[14].

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

- information is obtained from the water supplier that significant changes in the water supplied, such as seasonal variations, have occurred;
- significant deviations are observed in the process parameters, such as pH, conductivity, chlorine concentration and hardness, that can affect the performance of components of the water treatment system;
- reverse osmosis rejection rates decrease by more than 10 %.

All results of measurements of reverse osmosis performance should be recorded daily in an operating log that permits a review of trends and its historic.

7.3.8 Surveillance of deionization

Deionizers shall be monitored continuously using resistivity monitors that compensate for temperatures up to 25 °C and that are equipped with audible and visual alarms. Resistivity monitors shall have a minimum sensitivity of 1 MΩ·cm (1 μS/cm or 0,1 mS/m). If the resistivity of the water at the outlet of a deionizer is less than 1 MΩ·cm, the water shall not be used for dialysis. When deionization is employed as the primary method for removing inorganic contaminants (reverse osmosis is not employed) or when deionization is necessary to polish RO-treated water, chemical analyses to ensure that the requirements of [4.2.2](#) are met should be performed when the system is installed. Resistivity monitor readings should be recorded on a log sheet twice each treatment day.

7.3.9 Surveillance of bacteria and endotoxin-retentive filters

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

7.3.10 Surveillance of dialysis water storage and distribution

7.3.10.1 Surveillance of water storage tanks

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

For routine surveillance of a storage tank that supplies dialysis water to a central dialysis fluid delivery system, or when direct surveillance of a dialysis water storage tank is performed as part of a troubleshooting process, the total viable microbial count and endotoxin concentration should be determined using samples drawn from a port at the outlet of the storage tank. When a change has been made to an existing storage tank, more frequent testing should be considered to verify that bacteria or endotoxin levels are consistently within the allowed limits.

The need for additional testing should be based on the original validation plan (see [6.2](#)) and a risk analysis of the likely impact of the change on system performance. All total viable microbial counts and endotoxin results should be recorded on a log sheet and should be subject to trend analysis.