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Quality of dialysis fluid for haemodialysis and related therapies

Qualité des fluides de dialyse pour hémodialyse et thérapies apparentées

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Foreword

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

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

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

ISO 11663 was prepared by Technical Committee ISO/TC 150, *Implants for surgery*, Subcommittee SC 2, *Cardiovascular implants and extracorporeal systems*.

Introduction

Haemodialysis patients are directly exposed to large volumes of dialysis fluid, with the dialyser membrane being the only barrier against transfer of hazardous contaminants from the dialysis fluid to the patient. It has long been known that there could be hazardous contaminants in the water and concentrates used to prepare the dialysis fluid. To minimize this hazard, ISO 13958 and ISO 13959 set forth quality requirements for the water and concentrates used to prepare dialysis fluid. However, if the dialysis fluid is not prepared carefully, it could contain unacceptable levels of contaminants even though it is prepared from water and concentrates meeting the requirements of ISO 13958 and ISO 13959. Further, the dialysis fluid might be used as the starting material for the online preparation of fluids intended for infusion into the patient, for example, in therapies such as online haemodiafiltration. For these reasons, this International Standard for dialysis fluid quality was developed to complement the existing standards for water and concentrates, ISO 13959 and ISO 13958, respectively. Guidelines to aid the user in routinely meeting the requirements of this International Standard and ISO 13959 can be found in ISO 23500 [1].

This International Standard reflects the conscientious efforts of healthcare professionals, patients and medical device manufacturers to develop recommendations for the quality of dialysis fluid. This International Standard is directed at the healthcare professionals involved in the management of dialysis facilities and the routine care of patients treated in dialysis facilities, since they are responsible for the final preparation of dialysis fluid. The recommendations contained in this document are not intended for regulatory application.

The requirements of this International Standard aim to help protect haemodialysis patients from adverse effects arising from known chemical and microbiological contaminants that can be found in improperly prepared dialysis fluid. However, the physician in charge of dialysis has the ultimate responsibility for ensuring that the dialysis fluid is correctly formulated and meets the requirements of all applicable quality standards.

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

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

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

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

The concepts incorporated in this International Standard should not be considered inflexible or static. The recommendations presented here should be reviewed periodically in order to assimilate increased understanding of the role of dialysis fluid purity in patient outcomes and technological developments.

Quality of dialysis fluid for haemodialysis and related therapies

1 Scope

This International Standard specifies minimum requirements for dialysis fluids used for haemodialysis and haemodiafiltration, including substitution fluid for haemodiafiltration and haemofiltration. This International Standard does not address the requirements for the water and concentrates used to prepare dialysis fluid or the equipment used in its preparation. Those areas are covered by other ISO standards.

Excluded from the scope of this International Standard are sorbent-based dialysis fluid regeneration systems that regenerate and recirculate small volumes of dialysis fluid, systems for continuous renal replacement therapy that use prepackaged solutions, and systems and solutions for peritoneal dialysis.

2 Normative references

The following referenced documents are indispensable for the application 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 13958, *Concentrates for haemodialysis and related therapies*

ISO 13959, *Water for haemodialysis and related therapies*

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

3 Terms and definitions

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

3.1
acid concentrate
A-concentrate
acidified concentrated mixture of salts that, when diluted with dialysis water and bicarbonate concentrate, yields dialysis fluid for use in dialysis

NOTE 1 The term “acid” refers to the small amount of acid (usually acetic acid) that is included in the concentrate.

NOTE 2 Acid concentrate might contain glucose.

NOTE 3 Acid concentrate can be in the form of a liquid, a dry powder or a combination of the two.

3.2
action level
concentration of a contaminant at which steps should be taken to interrupt the trend toward higher, unacceptable levels

3.3
bicarbonate concentrate
B-concentrate
concentrated preparation of sodium bicarbonate that, when diluted with dialysis water and acid concentrate, makes dialysis fluid used for dialysis

NOTE 1 Sodium bicarbonate is also known as sodium hydrogen carbonate.

NOTE 2 Some bicarbonate concentrates also contain sodium chloride.

NOTE 3 Bicarbonate concentrate can be in the form of a liquid or a dry powder.

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

3.4
central dialysis fluid delivery system
system that produces dialysis fluid from dialysis water and concentrate or powder at a central point and distributes the dialysis fluid from the central point to individual dialysis machines

3.5
chlorine, total
sum of free and combined chlorine

NOTE chlorine can exist in water as dissolved molecular chlorine (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.

3.6
colony-forming unit
CFU
measure of bacterial or fungal cell numbers that theoretically arise from a single cell or group of cells when grown on solid media

NOTE Colonies can form from groups of organisms when they occur in aggregates.

3.7
dialysis fluid
aqueous fluid containing electrolytes and usually buffer and glucose, which is intended to exchange solutes with blood during haemodialysis

NOTE 1 The term “dialysis fluid” is used throughout this document to mean the fluid made from dialysis water and concentrates, which is delivered to the dialyser by the dialysis fluid delivery system. Such phrases as “dialysate”, “dialysis solution”, or “dialysing fluid” may be used in place of dialysis fluid.

NOTE 2 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 Dialysis fluid does not include prepackaged parenteral fluids used in some renal replacement therapies, such as haemodiafiltration and haemofiltration.

3.8
dialysis fluid delivery system
device that: (1) prepares dialysis fluid on line from dialysis water and concentrates or that stores and distributes premixed dialysis fluid; (2) circulates the dialysis fluid through the dialyser; (3) monitors the dialysis fluid for temperature, conductivity (or equivalent), pressure, flow and blood leaks; (4) prevents dialysis during disinfection or cleaning modes

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

NOTE 2 The dialysis fluid delivery system can be an integral part of the single patient dialysis machine or a centralized preparation system which feeds multiple bedside monitoring systems.

NOTE 3 Dialysis fluid delivery systems are also known as proportioning systems and dialysis fluid supply systems.

3.9
disinfection
destruction of pathogenic and other kinds of microorganisms by thermal or chemical means

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

NOTE 2 This definition of "disinfection" is equivalent to low-level disinfection in the Spaulding classification.

3.10
endotoxin
major component of the outer cell wall of gram-negative bacteria

NOTE Endotoxins are lipopolysaccharides, which consist of a polysaccharide chain covalently bound to lipid A. Endotoxins can acutely activate both humoral and cellular host defences, leading to a syndrome characterized by fever, shaking, chills, hypotension, multiple organ failure and even death if allowed to enter into circulation in a sufficient dose.

3.11
endotoxin units
EU
units assayed by the *Limulus* amoebocyte lysate (LAL) test when testing for endotoxins

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

NOTE 2 In some countries, endotoxin concentrations are expressed in international units (IU). Since the 1983 harmonization of endotoxin assays, EU and IU are equivalent.

3.12
haemodiafiltration
form of renal replacement therapy in which waste solutes are removed from blood by a combination of diffusion and convection through a high-flux membrane

NOTE Diffusive solute removal is achieved using a dialysis fluid stream as in haemodialysis. Convective solute removal is achieved by adding ultrafiltration in excess of that needed to obtain the desired weight loss; fluid balance is maintained by infusing a replacement solution into the blood either before the dialyser (pre-dilution haemodiafiltration) or after the dialyser (post-dilution haemodiafiltration).

3.13
haemodialysis
form of renal replacement therapy in which waste solutes are removed primarily by diffusion from blood flowing on one side of a membrane into dialysis fluid flowing on the other side

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

3.14
haemofiltration
form of renal replacement therapy in which waste solutes are removed from blood by convection

NOTE 1 Convective transport is achieved by ultrafiltration through a high-flux membrane. Fluid balance is maintained by infusing a replacement solution into the blood either before the haemofilter (pre-dilution haemofiltration) or after the haemofilter (post-dilution haemofiltration).

NOTE 2 There is no dialysis fluid stream in haemofiltration.

3.15
***Limulus* amoebocyte lysate test**
LAL test
assay used to detect endotoxin

NOTE The detection method uses the chemical response of the horseshoe crab (*Limulus polyphemus*) to endotoxin.

3.16
manufacturer
entity that designs, manufactures, fabricates, assembles, formulates or processes a finished device

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

3.17
microbiological contamination
contamination with any form of microorganism (e.g., bacteria, yeast, fungi and algae) or with the by-products of living or dead organisms such as endotoxins, exotoxins and cyanobacterial toxins (derived from blue-green algae)

3.18
non-pyrogenic
less than 0,03 EU/ml

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

3.19
sterile

free from viable microorganisms with a sterility assurance level (SAL) of 6

NOTE 1 “sterile” can be used to describe a packaged solution that was prepared using a terminal sterilization process that has been demonstrated to achieve a 10^{-6} microbial survivor probability, i.e., assurance of less than one chance in one million that viable microorganisms are present in the sterilized article.

NOTE 2 Alternatively, “sterile” can be used to describe a solution prepared for immediate use by a continuous process that has been validated to produce a solution free from viable microorganisms with a SAL of at least 6. This SAL applies to the total volume of solution used in a single application.

3.20
substitution fluid
fluid used in haemofiltration and haemodiafiltration treatments which is infused directly into the patient’s blood as a replacement for the fluid that is removed from the blood by filtration

NOTE 1 Substitution fluid is also referred to as substitution solution or replacement solution.

NOTE 2 Substitution fluid may also be used for bolus administration, for priming of extracorporeal blood circuit and for returning blood to the patient at the end of a treatment.

3.21
ultrapure dialysis fluid
highly purified dialysis fluid that can be used in place of conventional dialysis fluid or as feed solution for possible further processing to create fluid intended for infusion directly into the blood

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

3.22
user
physician or physician's representative responsible for the actual production and handling of dialysis fluid

NOTE This medical device International Standard is mainly directed to device manufacturers, and in that context the "user" is as noted above.

4 Requirements

4.1 Microbiological contaminants in dialysis fluid

4.1.1 General

The requirements contained in this clause apply to a sample of the dialysis fluid collected at the inlet to the dialyser or the reinfusion point.

4.1.2 Microbiological requirements for standard dialysis fluid

Standard dialysis fluid shall contain a total viable microbial count of less than 100 CFU/ml (when tested in accordance with Clause 5) and an endotoxin concentration of less than 0,5 EU/ml (when tested in accordance with Clause 5).

NOTE 1 The action level for the total viable microbial count in dialysis fluid should be 50 CFU/ml.

NOTE 2 If microbial counts exceeding the action levels are observed in the dialysis fluid, corrective measures, such as disinfection and retesting, should be taken promptly to reduce the levels.

4.1.3 Microbiological requirements for ultrapure dialysis fluid

Ultrapure dialysis fluid shall contain a total viable microbial count of less than 0,1 CFU/ml (when tested in accordance with Clause 5) and an endotoxin concentration less than 0,03 EU/ml (when tested in accordance with Clause 5). If those limits are exceeded in ultrapure dialysis fluid, corrective measures should be taken to reduce the levels to an acceptable range. The user is responsible for monitoring the dialysis fluid bacteriology of the system following installation. It is incumbent on the user to establish a regular monitoring routine.

4.1.4 Microbiological requirements for online prepared substitution fluid

The requirements contained in this clause apply to online prepared fluid intended to be infused into the patient as it enters the patient's blood.

This fluid shall be sterile and non-pyrogenic.

Substitution fluid for convective therapies, such as haemodiafiltration and haemofiltration, may be produced online by a process of ultrafiltration with bacteria and endotoxin retentive filters. This online-process shall be validated to produce fluid that is sterile and non-pyrogenic.

Compliance of online produced fluid with the requirements of this International Standard cannot be demonstrated with traditional test procedures. For this reason, compliance with this International Standard shall be ensured by proper operation of a validated system, verified according to the manufacturer's instructions at the time of installation, and confirmed by the user with a regular monitoring and maintenance schedule. The user shall follow the manufacturer's instructions for use of the validated system, and the user's monitoring and maintenance schedule shall be designed to confirm that the water and concentrates used to prepare the substitution fluid continue to meet the specifications of ISO 13958 and ISO 13959.