INTERNATIONAL STANDARD

ISO 13958

Second edition
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Concentrates for haemodialysis and related therapies

Concentrés 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 13958 was prepared by Technical Committee ISO/TC 150, *Implants for surgery*, Subcommittee SC 2, *Cardiovascular implants and extracorporeal systems*.

This second edition cancels and replaces the first edition (ISO 13958:2002), which has been technically revised.

Introduction

The requirements and goals established by this International Standard will help ensure the effective, safe performance of haemodialysis concentrates and related materials. This International Standard reflects the conscientious efforts of concerned physicians, clinical engineers, nurses, dialysis technicians and dialysis patients, in consultation with device manufacturers and government representatives, to develop a standard for performance levels that could be reasonably achieved at the time of publication. The term “consensus” as applied to the development of voluntary medical device standards does not imply unanimity of opinion, but rather reflects the compromise necessary in some instances when a variety of interests must be merged.

Throughout this International Standard, recommendations are made to use ISO-quality water. Therefore, it is recommended to review ISO 13959 along with this International Standard.

This International Standard does not cover the dialysis fluid that is used to clinically dialyse patients. Dialysis fluid is covered in ISO 11663. The making of dialysis fluid involves the proportioning of concentrate and water at the bedside or in a central dialysis fluid delivery system. Although the label requirements for dialysis fluid are placed on the labelling of the concentrate, it is the user's responsibility to ensure proper use.

In addition, this International Standard does not cover haemodialysis equipment, which is addressed in the new edition of IEC 60601-2-16.

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.

Concentrates for haemodialysis and related therapies

1 Scope

1.1 General

This International Standard specifies minimum requirements for concentrates used for haemodialysis and related therapies. For the purpose of this International Standard, “concentrates” are a mixture of chemicals and water, or a mixture of chemicals in the form of dry powder or other highly concentrated media, that are delivered to the end user to make dialysis fluid used to perform haemodialysis and related therapies. This International Standard is addressed to the manufacturer of such concentrates. In several instances in this International Standard, it became necessary to address the dialysis fluid, which is made by the end user, to help clarify the requirements for manufacturing concentrates. Because the manufacturer of the concentrate does not have control over the final dialysis fluid, any reference to dialysis fluid is for clarification and is not a requirement of the manufacturer.

1.2 Inclusions

This International Standard includes concentrates in both liquid and powder forms. Also included are additives, also called spikes, which are chemicals that may be added to the concentrate to increase the concentration of one or more of the existing ions in the concentrate and thus in the final dialysis fluid. This International Standard also gives requirements for equipment used to mix acid and bicarbonate powders into concentrate at the user's facility.

1.3 Exclusions

Concentrates prepared from prepackaged salts and water at a dialysis facility for use in that facility are excluded from the scope of this International Standard. Although references to dialysis fluid appear herein, this International Standard does not address dialysis fluid as made by the end user. Also excluded from the scope of this International Standard are requirements for the monitoring frequency of water purity used for the making of dialysis fluid by the dialysis facility. Recommendations from the technical committee responsible for this International Standard for monitoring water quality are contained in ISO 23500. This International Standard does not address bags of sterile dialysis fluid or sorbent dialysis fluid regeneration systems that regenerate and recirculate small volumes of the dialysis fluid.

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 13959, *Water for haemodialysis and related therapies*

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

IEC 61010-1:2001, *Safety requirements for electrical equipment for measurement, control, and laboratory use — Part 1: General requirements*

IEC 60601-1:2005, *Medical electrical equipment — Part 1: General requirements for basic safety and essential performance*

3 Terms and definitions

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

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

NOTE 1 Acetate concentrate might contain glucose.

NOTE 2 Sodium acetate is used to provide a buffer in place of sodium bicarbonate.

NOTE 3 Acetate concentrate is used as a single concentrate.

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

NOTE 1 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.

3.3
additive
spike
small amount of a single chemical that, when added to the concentrate, will increase the concentration of a single existing chemical by a value labelled on the additive packaging

3.4
batch system
apparatus in which the dialysis fluid is prepared in bulk before each dialysis session

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

NOTE 1 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.

3.6
bicarbonate dialysis fluid
dialysis fluid containing physiological or higher concentrations of bicarbonate

NOTE Bicarbonate dialysis fluid is generally produced from two concentrates: one containing bicarbonate and the other containing acid and other electrolytes. See **acid concentrate** (3.2) and **bicarbonate concentrate** (3.5).

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

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

3.8
bulk storage tank
large tank at the user's facility for storage of dialysis water or concentrate from bulk deliveries, or for concentrate prepared in bulk at the user's facility from powder and dialysis water

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

3.10
concentrate generator
system where the concentrate is delivered to the user as a powder in a container, suitable for attachment to the dialysis machine with which it is intended to be used, and then converted into a concentrated solution by the dialysis machine

NOTE The solution produced by the concentrate generator is used by the dialysis machine to make the final dialysis fluid delivered to the dialyser.

3.11
concentrate mixer
mixer for preparation of dialysis concentrate or dialysis fluid at a dialysis facility

3.12
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 haemodialfiltration and haemofiltration.

3.13
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 a 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.

3.14
dialysis water
water that has been treated to meet the requirements of ISO 13959 and which is suitable for use in haemodialysis applications, including the preparation of dialysis fluid, reprocessing of dialysers, preparation of concentrates and preparation of substitution fluid for online convective therapies

3.15
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 the circulation in a sufficient dose.

3.16
endotoxin units
EU
units assayed by the *Limulus* amoebocyte lysate (LAL) test when testing for endotoxins

NOTE 1 Because 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.

3.17
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.

3.18
***Limulus* amebocyte 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.

3.19
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.

3.20
proportioning system
apparatus that proportions dialysis water and haemodialysis concentrate to prepare dialysis fluid

3.21
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 Concentrates

4.1.1 Physical state

The concentrate for haemodialysis may be supplied in dry or aqueous form. Packaging may be for direct use with a single dialysis machine or for use in systems supplying multiple dialysis machines (bulk use).

4.1.2 Solute concentrations

4.1.2.1 Liquid solute concentrations

All electrolytes identified on the label shall be present within ± 5 % or ± 0,1 mEq/l (expressed as dialysis fluid concentrations), whichever is greater, of the stated concentration, with the exception of sodium, which shall be present within ± 2,5 % of the labelled concentration. Glucose shall be present within ± 5 % or ± 0,05 g/l (when measured as properly diluted dialysis fluid), whichever is greater, of the labelled concentration.

Where concentrates include non-traditional constituents, such as anti-oxidants and iron compounds, these constituents shall be present at nominal concentrations with ± 5 % tolerances.

Most concentrates are manufactured with standard traditional chemicals such as sodium chloride, potassium chloride, magnesium chloride, calcium chloride, acetic acid, glucose, etc. New concentrates are available on the market in which certain chemicals have been substituted by others; for example, citric acid has been substituted for acetic acid. Where this occurs, the labelling shall correctly reflect this and the substitute chemicals shall be present at nominal concentrations with ± 5 % tolerances.

4.1.2.2 Solute concentrations from powder

When concentrate is packaged in dry form or a combination of dry and liquid and is mixed according to the manufacturer's instruction for use, the final concentrate shall meet the requirements of 4.1.2.1.

4.1.3 Water

The quality of water used in the manufacture of the concentrate shall be in accordance with ISO 13959.

4.1.4 Bacteriology of concentrates

4.1.4.1 Bacteriology of bicarbonate concentrates

Concentrate containing bicarbonate supplied as a liquid shall be provided in a sealed container and manufactured by a process validated to produce dialysis fluid meeting the microbiological requirements of ISO 11663, when used according to the manufacturer's instructions. Bicarbonate powder intended for the preparation of concentrate at a dialysis facility shall be capable of producing dialysis fluid meeting the microbiological requirements of ISO 11663, when used according to the manufacturer's instructions.

4.1.4.2 Bacteriology of acid concentrates

There are no published reports of acid concentrate supporting bacterial growth and as such acid concentrate need not be tested for bacterial growth.

4.1.5 Endotoxin levels

The concentrate shall be formulated and packaged using a process validated to produce dialysis fluid meeting the endotoxin requirements of ISO 11663 or the applicable pharmacopoeia when used according to the manufacturer's instructions.

4.1.6 Fill volume

The excess fill volume of liquid and powder containers used with batch systems for a single dialysis treatment shall be within 2 % of the labelled volume. For non-batch use, the fill volume shall be $\geqslant$ 100 % of the stated volume.

4.1.7 Chemical grade

All chemicals shall meet the requirements of the applicable pharmacopoeia including all applicable portions of the general notices and of the general requirements for tests and assay. If all other requirements are met, monograph limits for sodium, potassium, calcium, magnesium and/or pH may be exceeded provided that correction is made, if necessary, for the presence of those ions in the final formulation. Also, any pharmacopoeia requirements that the chemicals be labelled for use in haemodialysis need not be complied with if the manufacturer is performing his own testing to meet the requirements of the applicable pharmacopoeia.

4.1.8 Particulates

The aqueous dialysis concentrate shall be filtered through a nominal 1 µm or finer particulate filter. The particulate filter used shall have a non-fibre-releasing membrane that does not contain material of known potential for human injury.

4.1.9 Additives — “spikes”

If additives are supplied, the concentration, when properly diluted with water or concentrate, shall yield values within ± 5 % by weight of the labelled value.

4.1.10 Containers

Containers, including the closures, shall not interact chemically or physically with the contents to alter the strength, purity or quality of the concentrate during handling, storage, and shipment. The containers shall have closures that prevent contamination or loss of content. Each container shall be marked to indicate its contents. One means of indicating the contents is to use an appropriate symbol (see Table 2).

4.1.11 Bulk delivered concentrate

When concentrate is delivered in bulk form, the responsibility for ensuring compliance with this International Standard shall pass from the manufacturer to the user at the legal point of transfer of the shipment. Once the concentrate is transferred from the manufacturer to the user, it becomes the user's responsibility to maintain the product in a usable state with appropriate labels and non-tamper procedures.

4.1.12 Concentrate generators

Concentrate generator systems include systems that mix powder, or powder and a highly concentrated liquid, into a concentrate by forming a slurry or concentrated solution in a container designed to function with specific dialysis machines. Mixing is accomplished by an automated dynamic proportioning system within the dialysis fluid delivery system. Because these concentrates are delivered to the user as a powder or a highly concentrated liquid in containers designed for specific machines, it is the concentrate generator manufacturer's responsibility to ensure that:

- all applicable clauses of this document dealing with powder are met;
- the container will function with the machines as defined by the manufacturers of the machines; and,
- undissolved powder is prevented from entering the dialysis fluid stream.

