INTERNATIONAL STANDARD

ISO 13958

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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 3.

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 International Standard may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

International Standard ISO 13958 was prepared by Technical Committee ISO/TC 150, *Implants for surgery*, Subcommittee SC 2, *Cardiovascular implants*.

Introduction

Dialysing fluids contain electrolytes in concentrations approaching that of the composition of normal extracellular body fluid. They can also contain non-electrolytes such as dextrose. Due to large volumes employed, dialysing fluids are generally prepared by diluting concentrates with water of suitable quality. Concentrates may be supplied in liquid or powder form.

Acid component concentrate for blending with bicarbonate, and acetate concentrate for use singly do not support bacterial growth. Bicarbonate concentrates can support bacterial growth. The preparation of bicarbonate concentrates should be made utilizing raw materials and techniques so that any microbial and chemical contamination is minimized. The concentrates should be stored in conditions that assure the maintenance of this low level.

During the dilution and use of these concentrates, precautions should be observed to minimize any microbial contamination.

The final dialysing fluids are produced from concentrates manufactured, packaged and labelled according to this International Standard, mixed with large proportions of water in accordance with ISO 13959. Operation of water treatment equipment and the handling of concentrates and the haemodialysis system are the responsibility of the haemodialysis facility.

Because these final mixed dialysing fluids are not within the control of manufacturers, this International Standard cannot address those vital clinical technical processes. Haemodialysis professionals make choices about the various applications (haemodialysis, haemodiafiltration, haemofiltration, reprocessing of devices) and need to understand the risks of each and the requirements for safety of fluids used for each therapy.

This International Standard is primarily directed at manufacturers of concentrates. However, it may also be used by haemodialysis facilities, which bear the ultimate responsibility for safe and appropriate use of dialysing fluid.

Concentrates for haemodialysis and related therapies

1 Scope

This International Standard is applicable to dry and liquid concentrates to be diluted for use as dialysing fluids in haemodialysis or haemodiafiltration. It addresses chemical quality and purity, microbial contamination, handling, measurement and labelling of concentrates, the requirements for containers and the tests to monitor concentrates.

This International Standard does not address the final mixing and use of these concentrates and treated water in such therapies. That operation is the sole responsibility of dialysis professionals.

This International Standard is not applicable to dialysing-fluid regeneration systems.

2 Normative reference

The following normative document contains provisions which, through reference in this text, constitute provisions of this International Standard. For dated references, subsequent amendments to, or revisions of, this publication do not apply. However, parties to agreements based on this International Standard are encouraged to investigate the possibility of applying the most recent edition of the normative document indicated below. For undated references, the latest edition of the normative document referred to applies. Members of ISO and IEC maintain registers of currently valid International Standards.

ISO 13959, *Water for haemodialysis and related therapies*

3 Terms and definitions

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

3.1
acetate dialysing fluid
dialysing fluid without bicarbonate, using acetate as a substitute

NOTE Acetate dialysing fluid is generally produced from a single concentrate.

3.2
anion
molecule or atom carrying a negative charge

3.3
batch system
system in which water and concentrate(s) are mixed in a batch, which is then used for haemodialysis or haemodiafiltration

3.4
bicarbonate dialysing fluid
dialysing fluid containing physiological or higher concentrations of bicarbonate and small quantities of sodium acetate

NOTE Bicarbonate dialysing fluid is produced by mixing two concentrates.

3.5
cation
molecule or atom carrying a positive charge

3.6
dialysing fluid
dialysis fluid
dialysate
fluid which is intended to exchange solutes with blood during haemodialysis or haemodiafiltration

NOTE It does not include infusion fluid used in haemodiafiltration.

3.7
electrolyte
any ion, or solution of ions, capable of conducting electricity

3.8
microbial
referring to microorganisms such as bacteria, fungi, etc.

NOTE The term bacteriology refers to the study of bacteria, a part of the broader field of microbiology.

3.9
proportioner
proportioning system
device for the continuous mixing of water and concentrates to produce dialysing fluid

3.10
pyrogen
fever-producing substance

NOTE Pyrogens are often lipopolysaccharides of bacterial origin.

3.11
non-pyrogenic
free of pyrogenic materials within the limits of error of test methods for such determinations (usually limulus lysate assay) and maintained in that state by suitable protection

3.12
sterile
free from viable microorganisms within the limits of validation tests for sterility (usually reduced 10^{-6}) and maintained in that state by suitable protection

4 Requirements

4.1 Solute concentrations

All solutes identified on the label shall be present within $\pm$ 5 % of the stated concentration, with the exception of sodium, which shall be present within $\pm$ 2,5 % of the stated concentration for the duration of the shelf-life of the product.

4.2 Water quality

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

4.3 Acidity or alkalinity

When the concentrate is diluted as directed on the label, the resulting acetate dialysing fluid shall have a pH in the range of 6,0 to 8,0.

4.4 Chemical grade

All chemicals shall meet the technical requirements of current regional and/or other appropriate national Pharmacopoeias, including all applicable portions of General Notices, and the general requirements for test and assay specified in applicable International Standards.

4.5 Filtration

Liquid acid or acetate concentrates shall be filtered through a 1,2 μm or finer, non-fibre-releasing filter that does not contain material of known potential for human injury. Bicarbonate concentrates shall be filtered through a similar 0,45 μm filter.

4.6 Containers

Containers, including the closures, shall not interact chemically or physically with their contents to alter concentrations beyond the limits and requirements of 4.1 and 4.2 during handling, storage and shipment. Each container shall include not less than 100 % of the labelled volume or mass. The container and closure shall maintain the microbiological quality and the volume of the contents.

4.7 Non-pyrogenicity

The concentrate shall be shown to be non-pyrogenic.

4.8 Sterility

If a statement on concentrate sterility is given, it shall be verified in accordance with 6.9.

5 Labelling and documentation requirements

5.1 General requirements

The label shall provide the following minimum information:

a) the name and address of the manufacturer and/or the distributor;

b) the expiration date (shelf life) expressed as yyyy/mm, where appropriate;

c) an identifying LOT number, which shall be capable of yielding the complete manufacturing history of the specific package, including all manufacturing and filling operations;

d) the composition, including additives, and the mass or concentration of each specified solute;

e) for concentrates for batch systems, the volumes of concentrate and water that shall be mixed;

f) for concentrates for proportioning systems, the proportion of each concentrate and water (liquid) that shall be mixed; proportioning ratios shall be prominently displayed on the label;

EXAMPLE The information can be given as 1:34.

g) the concentration of each electrolyte in the dialysing fluid (in millimoles per litre), the concentration of non-electrolytes in the dialysing fluid (in grams per litre) and the nominal measured final conductivity of the dialysing fluid [in millisiemens per centimetre (mS/cm)] at 25 °C;

h) a statement that the concentrate is non-pyrogenic;

i) a statement, where appropriate, that the concentrate is sterile and the method of sterilization;

j) the fill volume of the container;

k) the trade name of the product;

l) for concentrates which can support microbial growth (e.g. bicarbonate), a statement that the concentrate shall not be used for longer than the manufacturer's specified time after the container has been opened and first used;

m) a prominent statement that close inspection of containers and equipment shall be practised along with monitoring of the dialysis fluid to ensure that the appropriate concentrate(s) is being used.

NOTE Currently, no equipment exists which is adequate to protect the patient completely from misused concentrate producing inappropriate dialysis fluid. Careful attention to labels, connections and procedures by the professionals in attendance is essential for safety. The policies establishing this monitoring and the practices which assure it are the responsibility of the user.

5.2 Liquid concentrate

The label shall include the manufacturer's recommended storage conditions, including instructions not to use damaged containers or solutions with visible particulates.

5.3 Dry concentrate

The label shall include instructions to avoid exposure to excessive temperature (specified by the manufacturer) and to keep the container tightly sealed until use.

5.4 Colour coding

Means shall be provided for the user to readily distinguish between concentrates, e.g. acetate, bicarbonate or its acid counterpart. Caps and labels shall be white for acetate, blue for bicarbonate and red for acid concentrates.

6 Testing of concentrates

6.1 General

The test or measurement procedures below are to be regarded as reference procedures. Other procedures may be accepted, provided that the alternative procedure has been shown to be of comparable precision and reproducibility.

6.2 Solute concentrations

Compliance with 4.1 for calcium, magnesium and sodium shall be determined by the methods of ISO 13959. Compliance with the requirements for the other ingredients of the concentrate shall be determined as follows:

a) chloride: titration with silver electrode and potentiometric or conductometric end-point determination, titration with standardized silver nitrate;

b) acetate: gas chromatography or liquid chromatography;

c) glucose: polarimetry glucose oxidase or specific electrode;

d) bicarbonate: acid titration and calculation, or another method for determination of total CO_2.

6.3 Water quality

Compliance with the water quality requirements of 4.2 shall be determined in accordance with ISO 13959.

6.4 Acidity or alkalinity

The pH of the concentrate shall be determined by appropriate dilution of the concentrate with water in accordance with ISO 13959 and by measuring the pH with a suitably calibrated glass electrode having an accuracy of better than 0,1 pH units.

6.5 Chemical grade

The purity of chemicals shall be determined by tests outlined in regional and/or national Pharmacopoeias.

6.6 Filtration

Compliance shall be determined by inspection of the manufacturing records of the product.

6.7 Containers

Compliance with the requirements of 4.6 shall be determined by means of the tests for plastic containers described in regional and/or national Pharmacopoeias, and by appropriate volumetric or gravimetric techniques.

6.8 Non-pyrogenicity

Compliance shall be determined by the LAL assay for endotoxins, in which case the level of endotoxins in the concentrate shall not exceed 0,5 IU/ml when appropriately diluted with water in accordance with ISO 13959.

6.9 Sterility

Compliance with any statement on concentrate sterility shall be verified by manufacturer's documentation or by tests according to regional and/or national Pharmacopoeias.