BS EN ISO 1135-3:2017

BSI Standards Publication

Transfusion equipment for medical use

Part 3: Blood-taking sets for single use (ISO 1135-3:2016)

bsi.

National foreword

This British Standard is the UK implementation of EN ISO 1135-3:2017. It is identical to ISO 1135-3:2016.

The UK participation in its preparation was entrusted to Technical Committee CH/212, IVDs.

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

This publication does not purport to include all the necessary provisions of a contract. Users are responsible for its correct application.

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Compliance with a British Standard cannot confer immunity from legal obligations.

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EUROPEAN STANDARD

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English Version

Transfusion equipment for medical use - Part 3: Blood-taking sets for single use (ISO 1135-3:2016)

Matériel de transfusion à usage médical - Partie 3: Appareils non réutilisables pour prélèvement sanguin (ISO 1135-3:2016)

Transfusionsgeräte zur medizinischen Verwendung - Teil 3: Blutentnahmegeräte zur einmaligen Verwendung (ISO 1135-3:2016)

This European Standard was approved by CEN on 24 August 2016.

CEN members are bound to comply with the CEN/CENELEC Internal Regulations which stipulate the conditions for giving this European Standard the status of a national standard without any alteration. Up-to-date lists and bibliographical references concerning such national standards may be obtained on application to the CEN-CENELEC Management Centre or to any CEN member.

This European Standard exists in three official versions (English, French, German). A version in any other language made by translation under the responsibility of a CEN member into its own language and notified to the CEN-CENELEC Management Centre has the same status as the official versions.

CEN members are the national standards bodies of Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, Former Yugoslav Republic of Macedonia, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey and United Kingdom.

EUROPEAN COMMITTEE FOR STANDARDIZATION
COMITÉ EUROPÉEN DE NORMALISATION
EUROPÄISCHES KOMITEE FÜR NORMUNG

CEN-CENELEC Management Centre: Avenue Marnix 17, B-1000 Brussels

European foreword

This document (EN ISO 1135-3:2017) has been prepared by Technical Committee ISO/TC 76 “Transfusion, infusion and injection, and blood processing equipment for medical and pharmaceutical use” 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 August 2017, and conflicting national standards shall be withdrawn at the latest by August 2017.

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

This document has been prepared under a mandate given to CEN by the European Commission and the European Free Trade Association, and supports essential requirements of EU Directive(s).

For relationship with EU Directive(s), see informative Annex ZA, which is an integral part of this document.

According to the CEN-CENELEC Internal Regulations, the national standards organizations of the following countries are bound to implement this European Standard: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, Former Yugoslav Republic of Macedonia, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey and the United Kingdom.

The following referenced documents are indispensable for the application of this document. For undated references, the latest edition of the referenced document (including any amendments) applies. For dated references, only the edition cited applies. However, for any use of this standard "within the meaning of Annex ZA", the user should always check that any referenced document has not been superseded and that its relevant contents can still be considered the generally acknowledged state-of-art.

When an IEC or ISO standard is referred to in the ISO standard text, this shall be understood as a normative reference to the corresponding EN standard, if available, and otherwise to the dated version of the ISO or IEC standard, as listed below.

NOTE The way in which these referenced documents are cited in normative requirements determines the extent (in whole or in part) to which they apply.

Table 1— Correlations between undated normative references and dated EN and ISO standards

Normative references as listed in Clause 2 of the ISO standard	Equivalent dated standard	
	EN	ISO or IEC
ISO 3696	EN ISO 3696:1995	ISO 3696:1987
ISO 7864	EN ISO 7864:2016	ISO 7864:2016

ISO 11607-1	EN ISO 11607-1:2009 + A1:2014	ISO 11607-1:2006 plus ISO 11607-1 Amd 1:2014
ISO 14644-1:2015	EN ISO 14644-1:2015	ISO 14644-1:2015
ISO 15223-1	EN ISO 15223-1:2012	ISO 15223-1:2012

Endorsement notice

The text of ISO 1135-3:2016 has been approved by CEN as EN ISO 1135-3:2017 without any modification.

Annex ZA
(informative)

Relationship between this European standard and the essential requirements of Directive 93/42/EEC [OJ L 169] aimed to be covered

This European Standard has been prepared under a Commission's standardization request *'M/295 concerning the development of European standards related to medical devices'* to provide a voluntary means of conforming to essential requirements of Council Directive 93/42/EEC of 14 June 1993 concerning medical devices [OJ L 169].

Once this standard is cited in the Official Journal of the European Union under that Directive, compliance with the normative clauses of this standard given in Table ZA.1 confers, within the limits of the scope of this standard, a presumption of conformity with the corresponding essential requirements of that Directive, and associated EFTA regulations.

NOTE 1 Where a reference from a clause of this standard to the risk management process is made, the risk management process needs to be in compliance with Directive 93/42/EEC as amended by 2007/47/EC. This means that risks have to be reduced "as far as possible", "to a minimum", "to the lowest possible level", "minimized" or "removed", according to the wording of the corresponding essential requirement.

NOTE 2 The manufacturer's policy for determining **acceptable risk** must be in compliance with Essential Requirements 1, 2, 5, 6, 7, 8, 9, 11 and 12 of the Directive.

NOTE 3 This Annex ZA is based on normative references according to Table 1 of references in the European foreword, replacing the references in the core text.

NOTE 4 When an Essential Requirement does not appear in Table ZA.1, it means that it is not addressed by this European Standard.

Table ZA.1 — Correspondence between this European standard and Annex I of Directive 93/42/EEC [OJ L 169]

Essential Requirements of Directive 93/42/EEC	Clause(s)/subclause(s) of this EN	Remarks/Notes
7.2	3.3, 5.1, 5.2, 5.3, Clause 6, Clause 7, A.1, A.2	The part of ER 7.2 relating to packaging is not addressed (for packaging see Clause 9 of this standard).
7.3 (first part only)	Clause 4, 5.1, 5.2, 5.3, Clause 6, Clause 7, A.1, A.2	
7.5	5.2, 5.3, Clause 7, A.2	Only the first paragraph is covered. Presumption of conformity with the Essential Requirements relating to the biological evaluation can only be provided if the manufacturer chooses to apply the ISO 10993- series standards.

7.6	5.1, 5.2, 5.3, A.1, A.2	
8.1	3.4, 3.5, Clause 5	The part of ER 8.1 relating to handling is not addressed. Manufacturing processes are not covered. The reduction of the risk of infection is not fully covered.
8.3	3.3, 3.4, 5.9, Clause 9	
8.4	7.2	Only the sterilization method is covered.
8.5	5.1, A.1	
8.7	8.2, 8.3	
9.1	5.4, 5.5	The second sentence of ER 9.1 is not addressed. Coverage of this ER is partly provided by normative reference to EN ISO 7864.
9.2 (first indent)	Clause 5, 7.1	Covered in respect of the following: - Particulate contamination; - Leakage; - Tensile strength; - Dimensions; - Physical characteristics of tube and needle.
9.2 (second indent)	5.2	Covered in respect of the following: - Variations in pressure.
9.2 (fourth indent)	Clause 4	Covered in respect of the following: - Undesirable effects on blood or fluid used.
12.7.1	5.3	Only tensile strength is addressed.
13.1	Clause 8	Only requirements for labelling are covered.
13.2	8.1, 8.2, 8.3	The final sentence is not addressed.
13.3 b)	8.2 b), 8.3 b)	
13.3 c)	8.2 c), 8.3 c)	

13.3 d)	8.2 d), 8.3 d)	Only covered if the batch number is preceded by the word "LOT".
13.3 e)	8.2 e), 8.3 e)	
13.3 f)	8.2, 8.3	Requirement "indication of single use must be consistent across the Community" is not addressed in the standard.
13.4	8.2, 8.3	13.4 is addressed regarding to the label.

WARNING 1: Presumption of conformity stays valid only as long as a reference to this European standard is maintained in the list published in the Official Journal of the European Union. Users of this standard should consult frequently the latest list published in the Official Journal of the European Union.

WARNING 2: Other Union legislation may be applicable to the product(s) falling within the scope of this standard.

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Foreword

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

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

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

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

For an explanation on 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 the following URL: www.iso.org/iso/foreword.html.

The committee responsible for this document is ISO/TC 76, *Transfusion, infusion and injection, and blood processing equipment for medical and pharmaceutical use.*

This second edition cancels and replaces the first edition (ISO 1135-3:1986), which has been technically revised with the following changes:

— part title has been amended by "for single use" in alignment with the other parts of ISO 1135;

— figures have been updated;

— subclause 3.6, "Designation examples" has been deleted;

— physical, chemical and biological requirements have been aligned with ISO 1135-4;

— Clause 10, "Disposal" has been added;

— Annexes A, B and C have been aligned with ISO 1135-4;

— all references have been updated.

ISO 1135 consists of the following parts, under the general title *Transfusion equipment for medical use*:

— *Part 3: Blood-taking sets for single use*

— *Part 4: Transfusion sets for single use, gravity feed*

— *Part 5: Transfusion sets for single use with pressure infusion apparatus*

Transfusion equipment for medical use —

Part 3:
Blood-taking sets for single use

1 Scope

This part of ISO 1135 specifies requirements for types of blood-taking sets for medical use in order to ensure functional interchangeability of transfusion equipment. It is applicable to sterilized blood-taking sets intended for single use only.

This part of ISO 1135 also aims to provide

a) specifications relating to the quality and performance of materials used in transfusion equipment, and

b) a unified presentation of terms for such equipment.

In some countries, the national pharmacopoeia or other national regulations are legally binding and take precedence over this part of ISO 1135.

2 Normative references

The following documents, in whole or in part, are normatively referenced in this document and are indispensable for its application. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 3696:1987, *Water for analytical laboratory use — Specification and test methods*

ISO 7864, *Sterile hypodermic needles for single use*

ISO 11607-1, *Packaging for terminally sterilized medical devices — Part 1: Requirements for materials, sterile barrier systems and packaging systems*

ISO 14644-1:2015, *Cleanrooms and associated controlled environments — Part 1: Classification of air cleanliness by particle concentration*

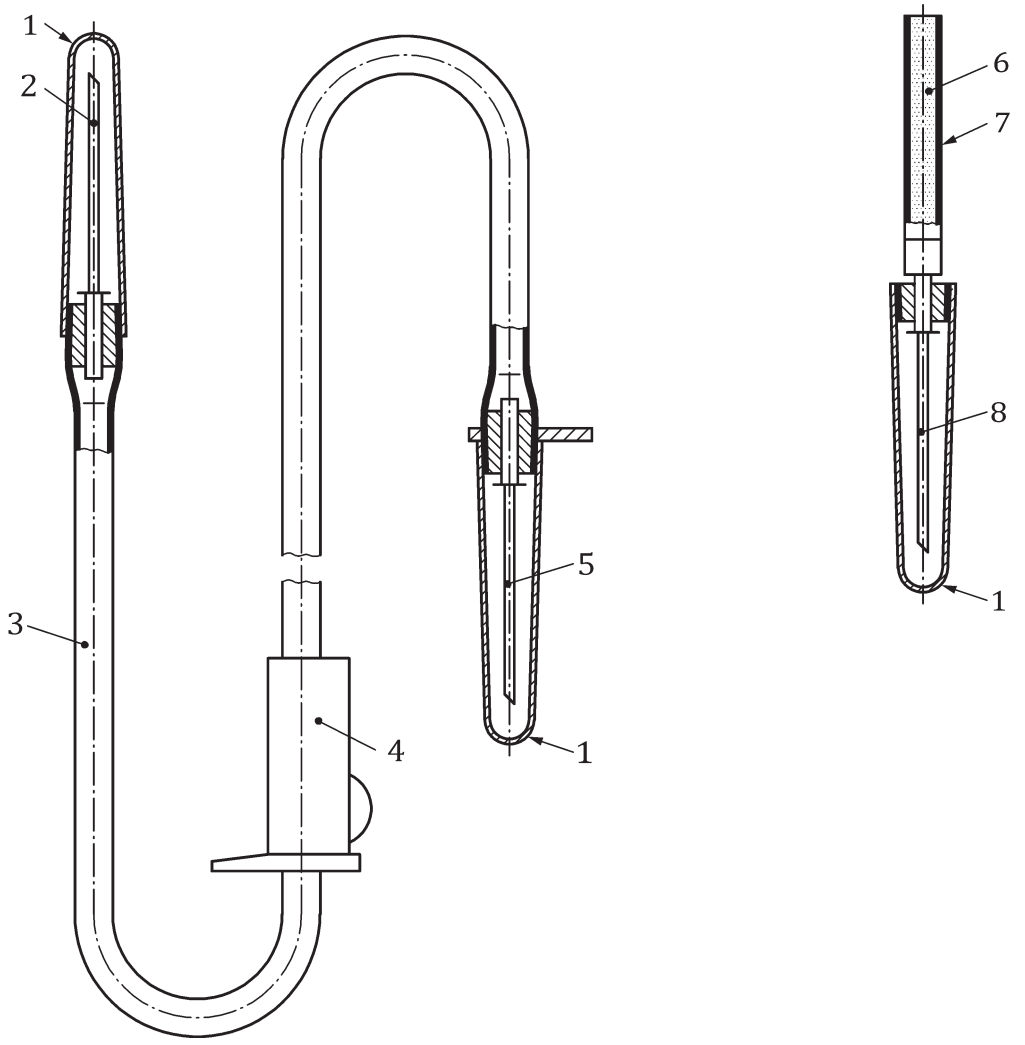
ISO 15223-1, *Medical devices — Symbols to be used with medical device labels, labelling and information to be supplied — Part 1: General requirements*

3 General requirements

3.1 Types of sets

The blood-taking set shall consist of the blood-taking assembly and the air-outlet assembly, which may be separate or combined.

A diagram of a typical blood-taking set is illustrated in Figure 1.



a) Blood-taking assembly **b) Air outlet assembly**

Key

1	protective cap	5	blood-taking needle
2	bottle needle	6	air filter
3	tubing	7	air filter housing
4	flow regulator (optional)	8	air-outlet needle

Figure 1 — Examples of typical blood-taking sets

3.2 Blood taking assembly

The blood-taking assembly shall consist of a blood-taking needle for vein puncture and of a bottle needle to be inserted through one of the specified areas provided on the bottle closure. Each needle is connected to one end of a length of tubing.

3.3 Air-outlet assembly

The air-outlet assembly shall consist of an air filter housing with air filter combined with an air-outlet needle for piercing the specified area provided on the bottle closure.

The filter shall be capable of preventing microbial ingress.

3.4 Sterilization

The blood-taking set shall be sterile in its unit container. Evidence of the effectiveness of the sterilization process used shall be provided.

3.5 Maintenance of sterility

The blood-taking set shall be provided with protective caps designed to maintain sterility of the internal surface of the set and the internal and external surfaces of the needles until the set is used.

4 Materials

The materials from which the blood-taking set is made shall not have undesirable effects on the blood passing through the set under ordinary conditions of use, or on the fluids used in connection with the blood. They shall not produce any general toxic effects or any local reaction on the recipient of the blood.

Appropriate type tests for assessing biological compatibility are given in Annex C.

5 Physical requirements

5.1 Particulate contamination

The blood-taking sets shall be manufactured under conditions that minimize particulate contamination. All parts shall be smooth and clean at the fluid pathway surfaces. When tested as specified in A.1, the number of particles detected shall not exceed the contamination index limit.

5.2 Leakage

The blood-taking set, when tested in accordance with A.2, shall show no signs of air leakage.

5.3 Tensile strength

Any connections between the components of the blood-taking set, excluding protective caps, shall withstand a static tensile force of not less than 15 N for 15 s.

5.4 Bottle needle

5.4.1 The bottle needle shall not be less than 35 mm in length. The external diameter shall not be less than 1,8 mm and the internal diameter shall not be less than 70 % of the external diameter.

5.4.2 The internal and external surfaces of the needle tube shall be clean and smooth.

5.4.3 The bottle needle shall be designed in accordance with ISO 7864 in order to minimize the number of rubber particles when the closure is pierced.

5.5 Air-outlet needle

The air-outlet needle shall have an internal diameter not less than 0,7 mm, an external diameter not greater than 1,9 mm and a needle not exceeding 25 mm in length.

5.6 Blood-taking needle

5.6.1 The blood taking needle shall not be less than 35 mm in length. The external diameter shall not be greater than 2 mm and the internal diameter shall not be less than 70 % of the external diameter.

5.6.2 The internal and external surface of the needle tube shall be clean and smooth. The bevel of the needle shall be sharp and free from ridges, burrs and barbs.

5.6.3 For further requirements on needles, see ISO 9626, DIN 13097-4 and DIN 13097-5.

5.7 Tubing

The tubing shall have an internal diameter of not less than 2,7 mm. It shall not be less than 600 mm in length. The tubing shall be flexible and shall not have any kinks.

5.8 Flow regulator

5.8.1 The flow regulator shall be capable of adjusting the flow of the blood between zero and the maximum.

5.8.2 The flow regulator shall be capable of continuous use throughout a donation without damaging the tubing. There shall be no deleterious reaction between the flow regulator and the tubing when stored in contact.

5.8.3 For further requirements on the flow regulator, see ISO 8536-14.

5.9 Protective caps

The protective caps at the end of the blood-taking set shall maintain the sterility or prevent contamination of the blood-taking needle, the bottle needle and the interior of the blood-taking set.

Protective caps should be secure but easily removable.

6 Chemical requirements

6.1 Reducing (oxidizable) matter

When tested in accordance with B.2, the difference of volume of $Na_2S_2O_3$ solution [$c(Na_2S_2O_3)$ = 0,005 mol/l] for the extract solution, S_1, and of volume of $Na_2S_2O_3$ solution for blank solution, S_0, shall not exceed 2,0 ml.

6.2 Metal ions

The extract shall not contain in total more than 1 µg/ml of barium, chromium, copper, lead and tin, and not more than 0,1 µg/ml of cadmium, when determined by atomic absorption spectroscopy (AAS) or an equivalent method.

When tested in accordance with B.3, the intensity of the colour produced in the test solution shall not exceed that of the standard matching solution containing (Pb^{2+}) = 1 µg/ml.

6.3 Titration acidity or alkalinity

When tested in accordance with B.4, not more than 1 ml of either standard volumetric solution shall be required for the indicator to change to the colour grey.

6.4 Residue on evaporation

When tested in accordance with B.5, the total amount of dry residue shall not exceed 5 mg.

6.5 UV absorption of extract solution

When tested in accordance with B.6, the extract solution S_1 shall not show absorbance greater than 0,1 (optical density).

7 Biological requirements

7.1 General

The blood-taking set shall not release any substances which may adversely affect the therapeutic effectiveness of the blood (see C.2).

7.2 Sterility

The blood-taking set in its unit container shall have been subjected to a validated sterilization process (see Bibliography).

7.3 Pyrogenicity

The blood-taking set shall be assessed for freedom from pyrogens using a suitable test and the results shall indicate that the blood-taking set is free from pyrogenicity. Testing for pyrogenicity shall be carried out in accordance with Annex C.

7.4 Haemolysis

The blood-taking set shall be assessed for freedom from haemolytic constituents and the result shall indicate that the blood-taking set is free from haemolytic reactions. Guidance on testing for haemolytic constituents is given in ISO 10993-4.

7.5 Toxicity

Materials shall be assessed for toxicity by carrying out suitable tests and the results of the tests shall indicate freedom from toxicity. Guidance on testing for toxicity is given in ISO 10993-1.

8 Labelling

8.1 General

The labelling shall include the requirements as specified in 8.2 and 8.3. If graphical symbols are used, then refer to ISO 3826-2 and ISO 15223-1.

NOTE The presence of substances of interest can be indicated by using symbol 2725 of ISO 7000 by replacing the “XXX” by the abbreviation of the substance. The absence of substances of interest can be indicated by crossing the respective symbol.

8.2 Unit container

The unit container shall be labelled at least with the following information using the graphical symbols in accordance with ISO 15223-1, where appropriate:

a) the name and address of the manufacturer;

b) description of the contents;

c) indication that the blood-taking set is sterile;

d) the lot (batch) designation;

e) year and month of expiry;

f) indication that the blood-taking set is for single use only, or equivalent wording;

g) instructions for use, including warnings, e.g. about detached protective caps and risk of air embolism when used inappropriately;

h) indication that the blood-taking set is free from pyrogens, or that the blood-taking set is free from bacterial endotoxins.

If the available space is too small to give all this information in legible characters and/or symbols, the information may be reduced to d) and e). In this case the information as required in this subclause shall be given on the label of the next bigger shelf or multi-unit container.

8.3 Shelf or multi-unit container

The shelf or multi-unit container, when used, shall be labelled at least with the following information using the graphical symbols in accordance with ISO 15223-1, where appropriate:

a) the name and address of the manufacturer;

b) description of the contents;

c) indication that the blood-taking sets are sterile;

d) the lot (batch) designation;

e) year and month of expiry;

f) the recommended storage conditions, if any;

g) the number of blood-taking sets.

9 Packaging

9.1 The blood-taking sets shall be individually packed so that the sets remain sterile during storage. Packaging shall follow ISO 11607-1.

The unit container shall be sealed in a tamper-evident manner.

9.2 The blood-taking sets shall be packed and sterilized so that there are no flattened portions or kinks when they are ready for use.

10 Disposal

Information for a secure and environmentally sound disposal of single-use blood-taking sets should be given, e.g. “Always dispose of blood contaminated products in a manner consistent with established biohazard procedures.”

Annex A
(normative)

Physical tests

A.1 Test for particulate contamination

A.1.1 Principle

The particles are rinsed from the inner fluid pathway surfaces of the blood-taking set, collected on a membrane filter and microscopically counted.

A.1.2 Reagents and materials

A.1.2.1 Distilled water, filtered through membrane of pore size 0,2 µm.

A.1.2.2 Non-powdered gloves.

A.1.2.3 Vacuum filter, single-membrane type of pore size 0,45 µm.

A.1.3 Procedure

The filter unit, filter and all other equipment shall be thoroughly cleaned before the test using distilled water (A.1.2.1).

Flush through each of 10 ready-to-use blood-taking sets, under laminar flow conditions (clean-air work station class N5 in accordance with ISO 14644-1:2015, Table 1) with 500 ml of distilled water (A.1.2.1). The total volume is subsequently vacuum filtered (A.1.2.3). Place the particles on the membrane screen filter under a microscope at 50× magnification using diagonally incident illumination, and measure and count them in accordance with the size categories given in Table A.1.

Table A.1 — Evaluation of contamination by particles

Particle parameters	Size category		
	1	2	3
Particle size in µm	25 to 50	51 to 100	over 100
Number of particles in 10 blood-taking sets	n_{a1}	n_{a2}	n_{a3}
Number of particles in the blank control sample	n_{b1}	n_{b2}	n_{b3}
Evaluation coefficient	0,1	0,2	5

A.1.4 Determination of results

A.1.4.1 General

An appropriate total number of single blood-taking sets (minimum of 10) are tested. The number of particles per 10 blood-taking sets tested in each of the three size categories is the assay result.

A.1.4.2 Particle counts

The values obtained from a blank control sample shall be recorded in a test report and taken into account when calculating the contamination index limit.

The blank control sample is the number and size of particles obtained from 10 equivalent 500 ml water samples classified in accordance with the three size categories set out in Table A.1, using the same test equipment but not passed through the appliances under test.

The number of particles in the blank, N_b, shall not exceed the value of 9. Otherwise the test apparatus shall be disassembled and re-cleaned, and the background test performed again. Values of the blank determination shall be noted in the test report.

The contamination index limit is calculated as follows.

For each of the three size categories, multiply the number of particles in 10 blood-taking sets by the evaluation coefficients, and add the results to obtain the number of particles in the blood-taking sets (test pieces), N_a. Then, for each of the size categories, multiply the number of particles in the blank control sample by the evaluation coefficients and add the results to obtain the number of particles in the blank sample, N_b.

Subtract N_b from N_a to obtain the contamination index limit.

Number of particles in the blood-taking sets (test pieces):

$$N_a = 0{,}1n_{a1} + 0{,}2n_{a2} + 5n_{a3} \quad \text{(A.1)}$$

Number of particles in the blank sample:

$$N_b = 0{,}1n_{b1} + 0{,}2n_{b2} + 5n_{b3} \quad \text{(A.2)}$$

Contamination index limit:

$$N = N_a - N_b \leq 90 \quad \text{(A.3)}$$

A.2 Test for leakage

A.2.1 At the beginning of the test, condition the whole system at the test temperature.

A.2.2 Immerse the blood-taking set, with one end blocked, in water at (40 ±1) °C and apply an internal air pressure of 50 kPa above atmospheric pressure for 15 s.

A.2.3 Examine the blood-taking set for air leakage.

Annex B
(normative)

Chemical tests

B.1 Preparation of extract solution, S_1, and blank solution, S_0

B.1.1 Extract solution, S_1

Assemble a closed circulation system composed of three sterilized blood-taking sets a 300 ml borosilicate glass boiling flask. Fit to the flask a thermostat device that maintains the temperature of the liquid in the flask at (37 ±1) °C. Circulate 250 ml of water, conforming to ISO 3696:1987, grade 1 or 2, through the system for 2 h at a rate of 1 l/h, for example using a peristaltic pump applied to a piece of suitable silicone tubing that is as short as possible.

Collect all of the extract solution, S_1, and allow to cool.

B.1.2 Blank solution, S_0

The blank solution, S_0, is prepared as described for the extract solution, S_1, but omitting the blood-taking sets from the circuit.

The extract solution, S_1, and the blank solution, S_0, shall be used for the chemical tests.

B.2 Tests for reducing (oxidizable) matter

Add 10 ml of extract solution, S_1, to 10 ml of potassium permanganate solution, $c(KMnO_4)$ = 0,002 mol/l, and 1 ml of sulfuric acid solution, $c(H_2SO_4)$ = 1 mol/l, agitate and allow to react for 15 min at (23 ±2) °C.

After 0,1 g of potassium iodide has been added, titrate the solution against a sodium thiosulfate standard volumetric solution, $c(Na_2S_2O_3)$ = 0,005 mol/l, until it turns light brown. Add 5 drops of starch solution and continue to titrate until the blue colour has disappeared.

Carry out a blank test simultaneously using the blank solution, S_0.

Calculate the difference of the volume of 0,005 mol/l $Na_2S_2O_3$ solution for the extract solution, S_1, and of the volume of $Na_2S_2O_3$ solution for the blank solution, S_0.

B.3 Test for metal ions

Test 10 ml of the extract solution, S_1, for metal ions, using procedures endorsed by the national pharmacopoeia. Determine the degree of coloration.

B.4 Test for titration acidity or alkalinity

Add 0,1 ml Tashiro indicator solution to 20 ml of extract solution, S_1, in a titration flask.

If the colour of the resulting solution is violet, titrate with sodium hydroxide standard volumetric solution, c(NaOH) = 0,01 mol/l, and if green, with hydrochloric acid standard volumetric solution, c(HCl) = 0,01 mol/l, until a greyish colour appears.

Express the volume of sodium hydroxide solution or hydrochloric acid solution used in millilitres.

B.5 Test for non-volatile residue

Transfer 50 ml of the extract solution, S_1, to a tared evaporating dish, and evaporate to dryness at a temperature just below the boiling point. Dry to constant mass at 105 °C.

Treat 50 ml of the blank solution, S_0, in the same manner.

Express the difference between the residual masses obtained from the extract solution, S_1, and the blank solution, S_0, in milligrams.

B.6 Test for absorbance

Pass the extract solution, S_1, through a membrane filter with pore size of 0,45 µm in order to avoid stray light interferences. Within 5 h of preparation, place the solution in a scanning UV spectrometer contained in a 1 cm quartz cell with the blank solution, S_0, in the reference cell, and record the spectrum in the wavelength range from 250 nm to 320 nm.

Report the result as a spectrum showing the absorbance plotted versus the wavelength.

Annex C
(normative)

Biological tests

C.1 Test on pyrogenicity

The test on pyrogenicity shall be carried out as described in national pharmacopoeias or national standards.

NOTE A test for pyrogens and bacterial endotoxins is described in the European Pharmacopoeia, in the United States Pharmacopeia and in the Japanese Pharmacopoeia.

C.2 Tests for biological evaluation

The test methods for biological evaluation as described in ISO 10993-1 should be considered as guidance when assessing biological compatibility.

Bibliography

[1] ISO 291, *Plastics — Standard atmospheres for conditioning and testing*

[2] ISO 594-1:1986[1)], *Conical fittings with a 6 % (Luer) taper for syringes, needles and certain other medical equipment — Part 1: General requirements*

[3] ISO 594-2:1998[1)], *Conical fittings with 6 % (Luer) taper for syringes, needles and certain other medical equipment — Part 2: Lock fittings*

[4] ISO 1773:1997, *Laboratory glassware — Narrow-necked boiling flasks*

[5] ISO 3826-2, *Plastics collapsible containers for human blood and blood components — Part 2: Graphical symbols for use on labels and instruction leaflets*

[6] ISO 7000, *Graphical symbols for use on equipment — Registered symbols*

[7] ISO 8536-14, *Infusion equipment for medical use — Part 14: Clamps and flow regulators for transfusion and infusion equipment without fluid contact*

[8] ISO 9626, *Stainless steel needle tubing for the manufacture of medical devices*

[9] ISO 10993-1, *Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process*

[10] ISO 10993-4, *Biological evaluation of medical devices — Part 4: Selection of tests for interactions with blood*

[11] ISO 11135, *Sterilization of health-care products — Ethylene oxide — Requirements for the development, validation and routine control of a sterilization process for medical devices*

[12] ISO 11137 (all parts), *Sterilization of health care products — Radiation*

[13] ISO 17665-1, *Sterilization of health care products — Moist heat — Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices*

[14] IEC 80416-1, *Basic principles for graphical symbols for use on equipment — Part 1: Creation of graphical symbols for registration*

[15] DIN 13097-4, *Hypodermic needles — Part 4: Point geometry, requirements and testing*

[16] DIN 13097-5, *Hypodermic needles — Part 5: Sockets, hubs and connections — Requirements and testing*

[17] European Pharmacopoeia

[18] United States Pharmacopeia

[19] Japanese Pharmacopoeia

1) Will be replaced by ISO 80369-7.

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