INTERNATIONAL STANDARD

ISO 3826-4

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Plastics collapsible containers for human blood and blood components —

Part 4: Aphaeresis blood bag systems with integrated features

Poches en plastique souple pour le sang et les composants du sang —

Partie 4: Systèmes de poches d'aphérèse pour le sang avec accessoires intégrés

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Contents

Page

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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 WTO principles in the Technical Barriers to Trade (TBT) see the following URL: Foreword - Supplementary information

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

ISO 3826 consists of the following parts, under the general title *Plastics collapsible containers for human blood and blood components*:

— *Part 1: Conventional containers*

— *Part 2: Graphical symbols for use on labels and instruction leaflets*

— *Part 3: Blood bag systems with integrated features*

— *Part 4: Aphaeresis blood bag systems with integrated features*

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Introduction

In some countries, national pharmacopoeias or other government regulations are legally binding and these requirements take precedence over this part of ISO 3826.

The manufacturers of the plastics container or the suppliers are expected to disclose in confidence to the national control authority, if requested by them, full details of the plastics material(s) and the components of the materials and their methods of manufacture, details of manufacture of the plastics containers including the chemical names and quantities of any additives, whether incorporated by the manufacturer of the plastics containers or present in the raw material, as well as full details of any additives that have been used.

Universal leucocyte depletion is mandatory in various countries. This part of ISO 3826 is considered a basic document for other standards which include technical innovations.

The requirements in this part of ISO 3826 are intended to

a) ensure that the quality of blood and blood components is maintained as high as necessary,

b) make possible efficient and safe collection, identification, storage, separation, and transfusion of the contents with special attention to reducing or minimizing the risks resulting from

   — contamination, in particular microbiological contamination,

   — air embolism,

   — errors in identification of plastics containers and any representative samples of contents, and

   — interaction between the plastics container and its contents,

c) ensure functional compatibility when used in combination with transfusion sets as specified in ISO 1135-4 and ISO 1135-5, and

d) provide a package with appropriate resistance to breakage and deterioration.

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Plastics collapsible containers for human blood and blood components —

Part 4: Aphaeresis blood bag systems with integrated features

1 Scope

This part of ISO 3826 specifies requirements including performance requirements for aphaeresis blood bag systems with integrated features. Aphaeresis blood bag systems need not contain all of the integrated features identified in this part of ISO 3826.

The integrated features refer to:

— needle stick protection device;

— leucocyte filter;

— sterile barrier filter;

— pre-collection sampling device;

— red blood cell storage bag;

— plasma storage bag;

— platelet storage bag;

— polymorphonucleic (e.g. stem) cell storage bag;

— post-collection sampling devices; and

— connections for storage solutions, anticoagulant, and replacement fluid.

This part of ISO 3826 specifies additional requirements for blood bag systems used to collect varying quantities of blood components or cells by apheresis. This part of ISO 3826 can be used on automated or semi-automated blood collection systems.

In some countries, the national pharmacopoeia or other national regulations are legally binding and take precedence over this part of ISO 3826.

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

ISO 1135-4, *Transfusion equipment for medical use — Part 4: Transfusion sets for single use*[2)]

1) Will be replaced by ISO 80369-7.

2) Will be split up in two parts of which the revised ISO 1135-4 covers transfusion sets for single use, gravity feed and the new ISO 1135-5 covers transfusion sets for single use with pressure infusion apparatus.

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

ISO 3826-1, *Plastics collapsible containers for human blood and blood components — Part 1: Conventional containers*

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

ISO 3826-3, *Plastics collapsible containers for human blood and blood components — Part 3: Blood bag systems with integrated features*

ISO 8536-4, *Infusion equipment for medical use — Part 4: Infusion sets for single use, gravity feed*

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

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

ISO 10993-5, *Biological evaluation of medical devices — Part 5: Tests for in vitro cytotoxicity*

ISO 10993-10, *Biological evaluation of medical devices — Part 10: Tests for irritation and skin sensitization*

ISO 10993-11, *Biological evaluation of medical devices — Part 11: Tests for systemic toxicity*

ISO 10993-12, *Biological evaluation of medical devices — Part 12: Sample preparation and reference materials*

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

ISO 15747, *Plastic containers for intravenous injections*

ISO 23908, *Sharps injury protection — Requirements and test methods — Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling*

3 Terms and definitions

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

3.1
aphaeresis (apheresis)
process by which blood being removed from a subject is immediately separated into component parts, usually to allow a desired component or components to be retained while the remainder is returned to the subject

3.2
aphaeresis set
whole aphaeresis blood bag system with integrated features

Note 1 to entry: Can also be called an aphaeresis kit or harness.

3.3
centrifugation
process in which circular motion is applied to a chamber about a central axis such that the fluid contents of the chamber are separated according to density where the most dense is towards the outer circumference of motion and the least dense is towards the inner circumference of motion

3.4
connector
component that allows one part of the set to be connected to another

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3.5
citrate anticoagulant
citrate, in the form of sodium citrate or acid-citrate-dextrose, is added to the blood as it is drawn from the subject's circulation and binds or chelates ionised calcium within the blood, thereby, impeding those steps of the coagulation pathway that are dependent on the presence of ionised calcium

3.6
clamp
device that prevents the flow of fluid through the lumen

Note 1 to entry: These can be locking (permanent) or non-locking (temporary).

3.7
extracorporeal circuit
path followed by whole blood or blood components when they are outside the subject's circulation

3.8
fluid pathway
route along which fluids (whole blood, blood components, ancillary intravenous solutions) pass composed of tubing, chambers, *connectors* (3.4) and pressure sensors, and needles

Note 1 to entry: The fluid pathway is constructed to ensure that the fluid within it remains sterile and to ensure that there are no restrictions or obstructions within it that might result in cellular damage or activation of the coagulation cascade.

3.9
leucocyte filter
filter used to reduce the content of leucocytes in blood or blood components

3.10
pilot sample
sample of unmistakable identity to be used for testing

3.11
plasma
blood plasma is a liquid component of blood

Note 1 to entry: It makes up of about 55 % of total blood volume.

3.12
plastics container
bag of plastic material complete with collecting tube and needle, port(s), anticoagulant and/or preservative solutions, and transfer tube(s) and associated container(s) where applicable

3.13
platelets
platelets or thrombocytes are small, irregularly shaped, clear cells with no nucleus involved in haemostasis leading to the formation of blood clots

3.14
platelet additive solution
PAS
solution in which *platelets* (3.13) are suspended

3.15
red blood cell additive solution
RAS
solution added to packed red cells to increase the storage life of red blood cells and prevent haemolysis

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3.16
platelet storage bag
PSB
bag suitable for appropriate storage of a therapeutic dose of platelet concentrates obtained from a single donation

3.17
red blood cell storage bag
bag suitable for storage of a therapeutic dose of red cells obtained from a single donation

3.18
pre-collection sampling device
device integrated in the collect line of blood collection systems or aphaeresis disposable sets designed to allow blood samples to be obtained at the beginning of a collection procedure without breaching the sterility of the collected components

Note 1 to entry: Usually incorporates a small reservoir from which the required blood samples are withdrawn. If a skin plug is obtained at the point of venepuncture, it is likely to be trapped in the reservoir rather than being drawn into the collected component(s), thereby, reducing the risk of bacterial contamination of the collected component(s).

Note 2 to entry: Also called PDS (pre-donation sampling device).

3.19
post-collection sampling device
device that can be integrated to allow a blood component sample to be taken, for example, for sterility testing or bacterial screening

3.20
needlestick protection device
NPD
device integrated in the donor line of blood bag systems containing the donor needle and designed to prevent undesirable needle sticks after use of the donor needle

Note 1 to entry: See ISO 23908.

3.21
replacement fluid
fluid used during an aphaeresis procedure to replace some or all of the blood volume associated with the collected components

3.22
anticoagulant safety connector
connector (3.4) specifically intended for use with *citrate anticoagulant* (3.5) to prevent accidental misconnection of anticoagulant with *replacement fluid* (3.21)

Note 1 to entry: An appropriate ISO standard is under preparation (ISO 18250-8).

3.23
shelf-life
period between the date of sterilization and the expiry date after which the sets should not be used

3.24
sterile barrier filter
filter intended to prevent micro-organisms or bacteria from entering a sterile *fluid pathway* (3.8)

4 Dimensions

Figure 1, Figure 2, Figure 3, and Figure 4 illustrate the components of an aphaeresis blood bag system with integrated features. The general drawings and the drawing of each feature are for guidance only.

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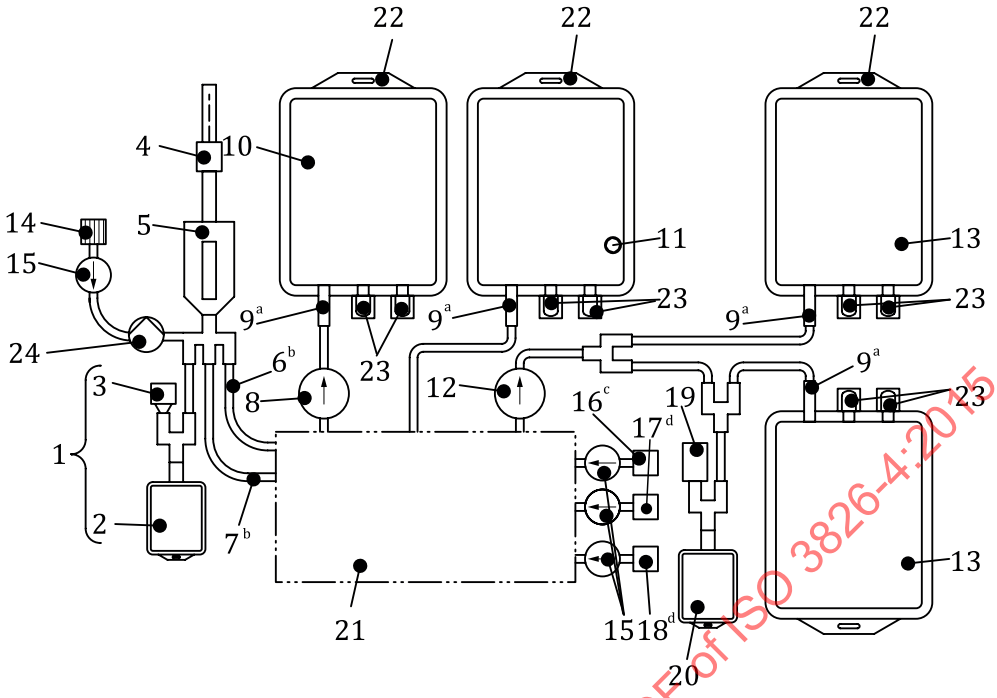

Key

1	pre-collection sampling device	15	sterile barrier filter
2	pre-collection sampling container	16	replacement fluid line if applicable to the set shall be provided with spike in accordance with ISO 8536-4 or a needle for fluid containers with narrow septums
3	multiple sampling device	17	red cell additive solution (RAS) connection to the extracorporeal circuit - male luer in accordance with ISO 594-2
4	access and return line needle (or connection device)	18	platelet additive solution (PAS) connection to the extracorporeal circuit - female luer in accordance with ISO 594-2
5	needle stick protection device (NPD)	19	bacterial sampling port
6	access line to aphaeresis extracorporeal circuit from donor or patient	20	post-collection sample container
7	return line from aphaeresis extracorporeal circuit to donor or patient	21	aphaeresis extracorporeal circuit (not covered by this part of ISO 3826)
8	leucocyte filter for red blood cells (LCF)	22	hanger eyelet
9	inlet port	23	outlet port
10	red blood cell storage bag	24	anticoagulant metering pump
11	plasma storage bag	a	Means of closure. The means can be positioned at other sites.
12	leucocyte filter for platelets (LCF)	b	The position of the lines can be different than depicted.
13	platelet storage bag (PSB)	c	Spike design is defined in ISO 8536-4.
14	anticoagulant safety connector for citrate anticoagulant	d	Additive (preservative) solution lines are optional and can be different than depicted.

Figure 1 — Schematic representation of components of a single needle donor aphaeresis blood bag system with integrated features — red cell blood bag with in-line leucocyte filter, platelet storage bag with in-line leucocyte filter, and pre-/post-donation sampling

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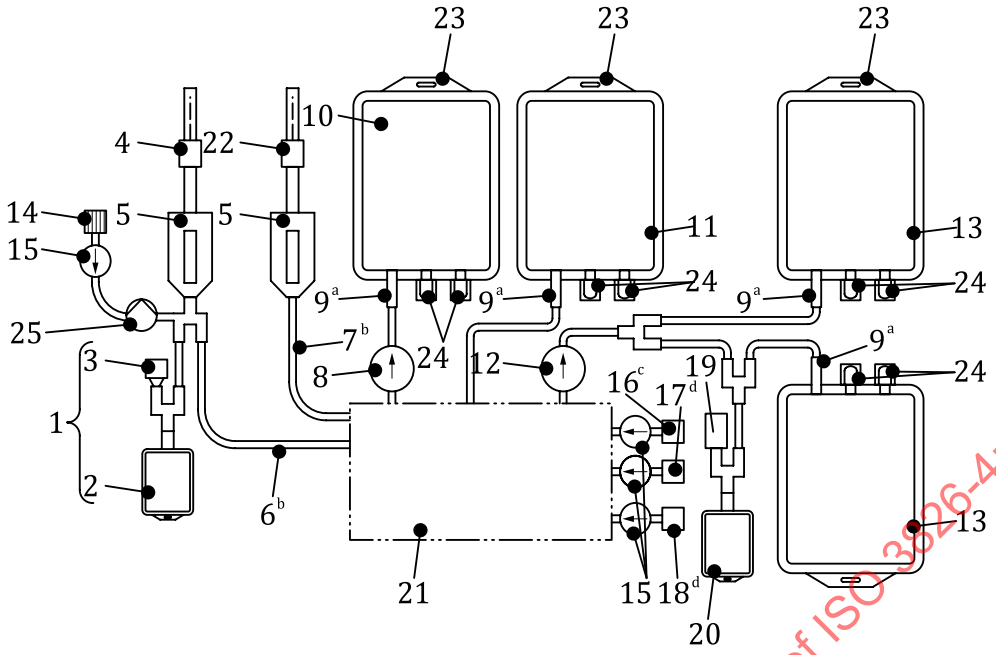

Key

1	pre-collection sampling device	16	replacement fluid line if applicable to the set shall be provided with spike in accordance with ISO 8536-4 or a needle for fluid containers with narrow septums
2	pre-collection sampling container	17	red cell additive solution (RAS) connection to the extracorporeal circuit - male luer in accordance with ISO 594-2
3	multiple sampling device	18	platelet additive solution (PAS) connection to the extracorporeal circuit - female luer in accordance with ISO 594-2
4	access line needle (or connection device)	19	bacterial sampling port
5	needle stick protection device (NPD)	20	post-collection sample container
6	collect line to aphaeresis extracorporeal circuit from donor or patient	21	aphaeresis extracorporeal circuit (not covered by this part of ISO 3826)
7	return line from aphaeresis extracorporeal circuit to donor or patient	22	return line needle (or connection device)
8	leucocyte filter for red blood cells (LCF)	23	hanger eyelet
9	bag inlet	24	outlet port
10	red blood cell storage bag	25	anticoagulant metering pump
11	plasma storage bag	a	Means of closure. The means can be positioned at other sites.
12	leucocyte filter for platelets (LCF)	b	The position of the lines can be different than depicted.
13	platelet storage bag (PSB)	c	Spike design is defined in ISO 8536-4.
14	anticoagulant safety connector for citrate anticoagulant	d	Additive (preservative) solution lines are optional and can be different than depicted.
15	sterile barrier filter		

Figure 2 — Schematic representation of components of a dual needle donor aphaeresis blood bag system with integrated features — red cell blood bag with in-line leucocyte filter, platelet storage bag with in-line leucocyte filter, and pre-/post-donation sampling devices

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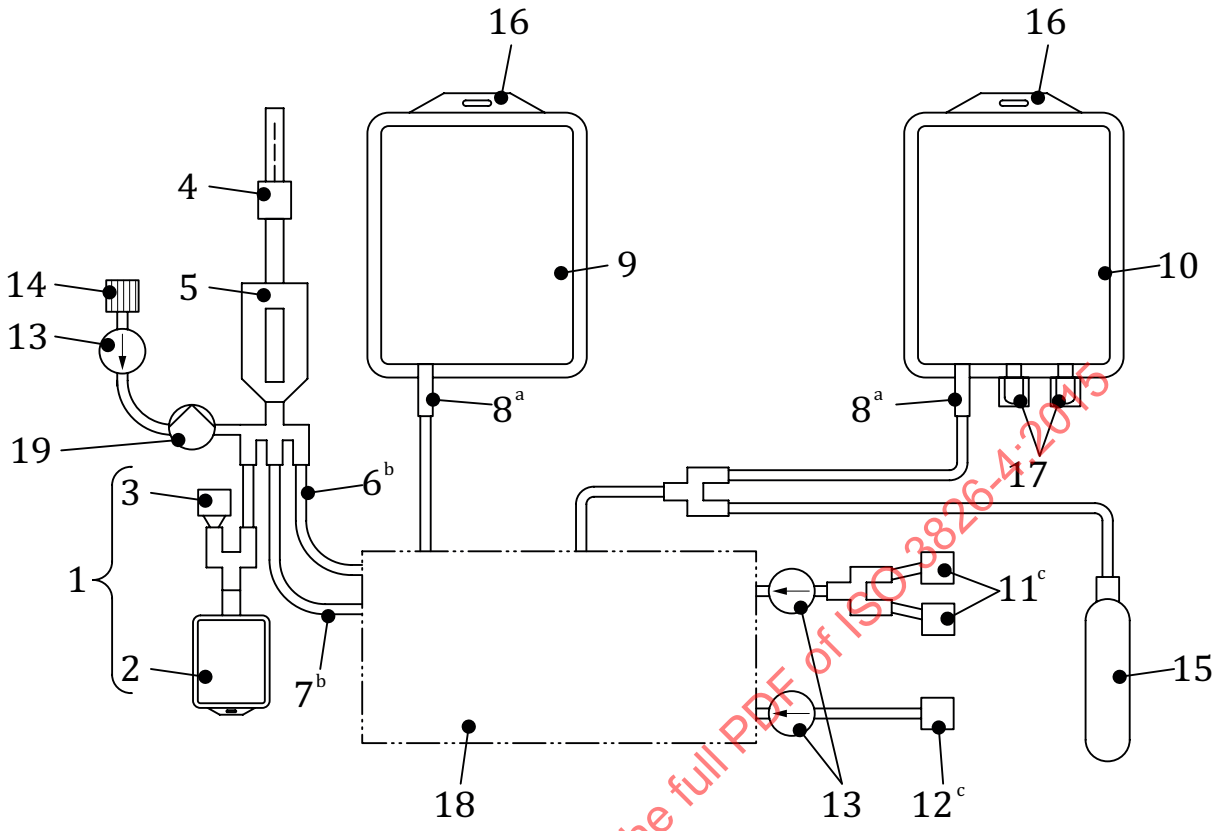

Key

1	pre-collection sampling device	12	replacement fluid line with spike in accordance with ISO 8536-4 or a needle for fluid containers with narrow septums
2	pre-collection sampling container	13	sterile barrier filter
3	multiple sampling device	14	anticoagulant safety connector for citrate anticoagulant
4	access and return line needle	15	sample bulb
5	needle stick protection device (NPD)	16	hanger eyelet
6	collect line to aphaeresis extracorporeal circuit from donor or patient	17	outlet port
7	return line from aphaeresis extracorporeal circuit to donor or patient	18	aphaeresis extracorporeal circuit (not covered by this part of ISO 3826)
8	inlet port	19	anticoagulant metering pump
9	waste bag	a	Means of closure. The means can be positioned at other sites.
10	cell collection bag (may be multiples)	b	The position of the lines can be different than depicted.
11	saline fluid lines with spike in accordance with ISO 8536-4	c	Spike design is defined in ISO 8536-4.

Figure 3 — Schematic representation of components of a single needle therapeutic aphaeresis blood bag system with integrated features — cell collection bag, waste bag, and pre-/post-collection sampling

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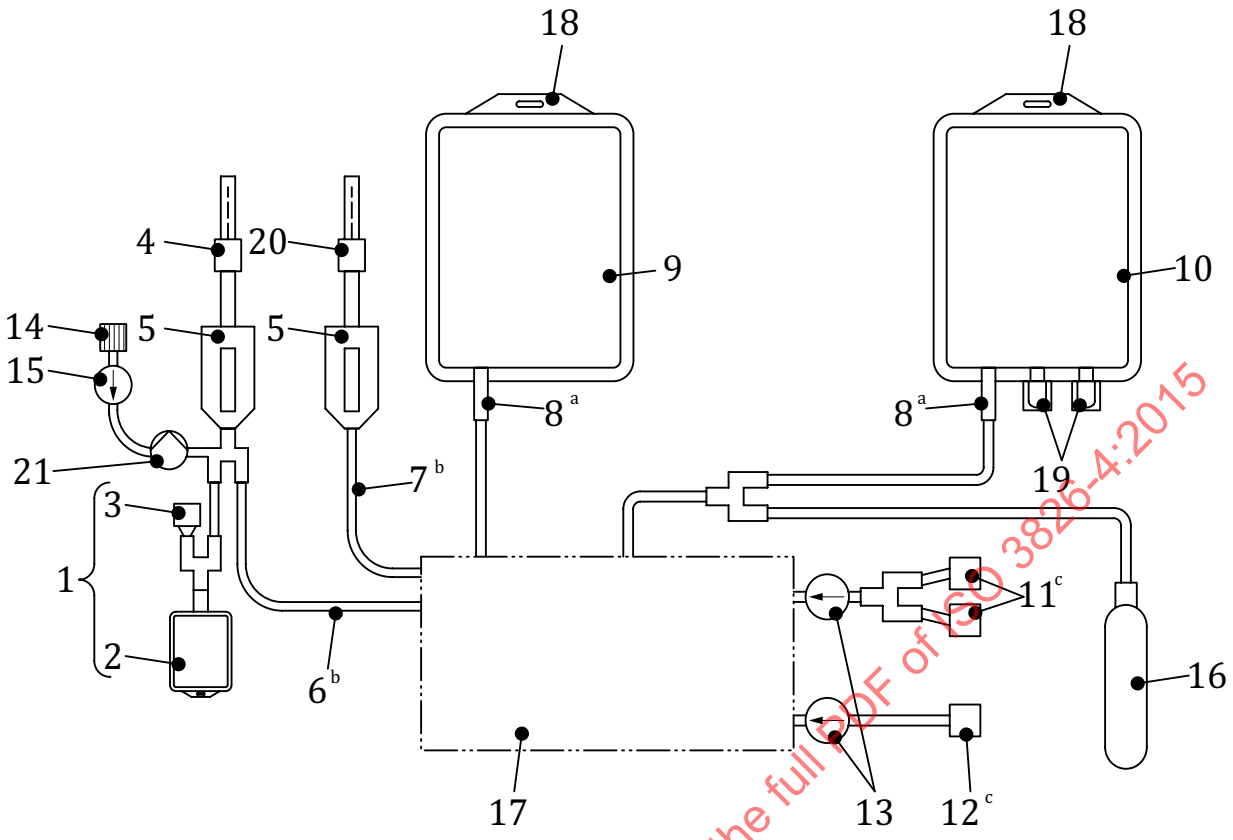

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Key

1	pre-collection sampling device	13	sterile barrier filter
2	pre-collection sampling container	14	anticoagulant safety connector for citrate anticoagulant
3	multiple sampling device	15	sterile barrier filter
4	access line needle	16	sample bulb
5	needle stick protection device (NPD)	17	aphaeresis extracorporeal circuit (not covered by this part of ISO 3826)
6	collect line to aphaeresis extracorporeal circuit from donor or patient	18	hanger eyelet
7	return line from aphaeresis extracorporeal circuit to donor or patient	19	outlet port
8	inlet port	20	return line needle
9	waste bag	21	anticoagulant metering pump
10	cell collection bag (may be multiples)	a	Means of closure. The means can be positioned at other sites.
11	saline fluid lines with spike in accordance with ISO 8536-4	b	The position of the lines can be different than depicted.
12	replacement fluid line with spike in accordance with ISO 8536-4 or a needle for fluid containers with narrow septums	c	Spike design is defined in ISO 8536-4.

Figure 4 — Schematic representation of components of a dual needle therapeutic aphaeresis blood bag system with integrated features — cell collection bag, waste bag, and pre-/post-collection sampling

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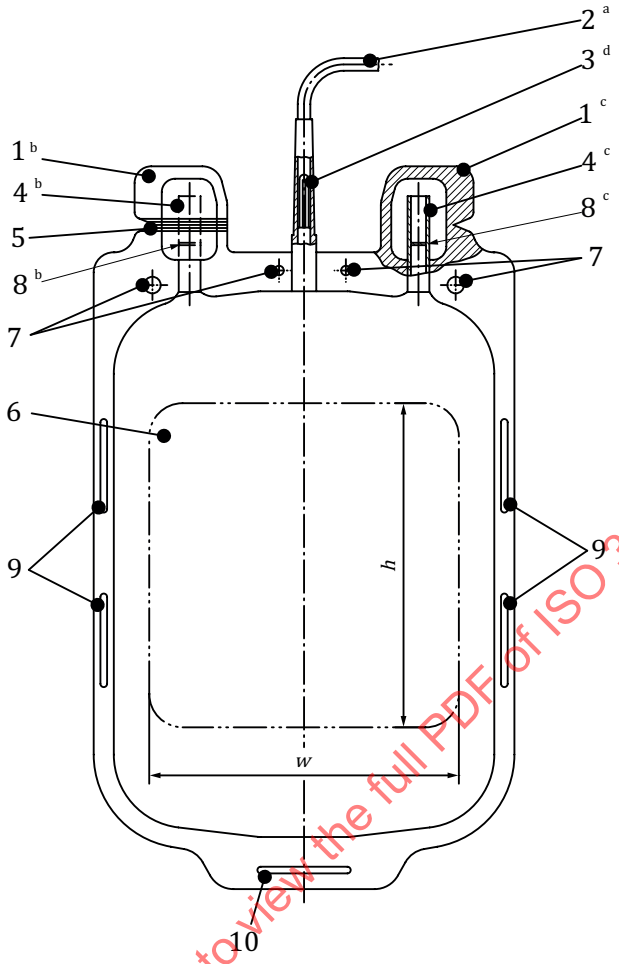

Key

1	tamper evident protector(s)	8	puncturable non-resealable closure(s) (optional)
2	fill tube	9	side slits (optional)
3	bag inlet	10	hanger eyelet
4	outlet port(s)	a	Internal diameter ≥ 2,7 mm, wall thickness ≥ 0,5 mm.
5	tear line of protector	b	External view.
6	label area	c	Cross-sectional view.
7	eyelets (optional)	d	Means of closure can be located elsewhere (optional).

NOTE See Table 1 for explanation of dimensions.

Figure 5 — Schematic representation of plastics container

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Table 1 — Dimensions for label areas and nominal capacity for component bags

Dimensions in millimetres

Storage Capacity	Size of label area	
ml	$w \pm 5$	$h \pm 5$
100	60	85
250	90	85
400	105	105
500/600	105	105

Dimensions in millimetres

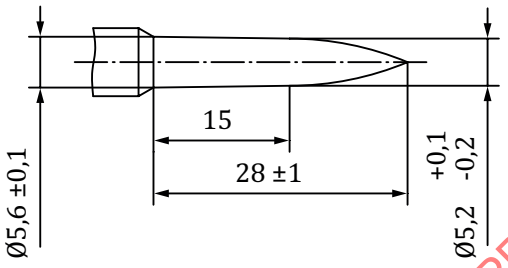

Figure 6 — Dimensions of the closure-piercing device (extracted from ISO 1135-4)

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5 Design

5.1 Leucocyte filter

5.1.1 When provided as an integrated feature, the leucocyte filter is integrated in plastic container(s) as a blood component filter. It is designed to reduce the leucocyte content of one blood component unit. The filters can be designed to work by gravity or pressure filtration at 4 °C or ambient temperature, depending on manufacturer's specifications.

NOTE Leucocyte filters might be subjected to national requirements and standards.

5.1.2 Where provided as part of the integrated features, manufacturers shall give recommendations for the intended use of the leucocyte filters considering parameters including

— capacity of the leucocyte filter,

— leucoreduction efficiency,

— blood component filtration temperature,

— filtration height, and

— use of pressure.

5.2 Pilot samples

For donor aphaeresis blood bag systems with an integrated red blood cell storage bag, the plastics container can be designed so that pilot samples of unmistakable identity can be collected for the

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performance of compatibility tests without the closed system of the plastics container being penetrated. This can be accomplished, for example, by using an unmistakable numbering system on the tubing.

NOTE The number of segments for pilot samples can be defined in national regulations.

5.3 Access line needle and return line needle

5.3.1 Where provided, the access and return line needle shall be fitted with a protective cover. The protective cover shall maintain the sterility of the fluid path and shall be readily removable.

5.3.2 For therapeutic aphaeresis, the access or return line needle can be removable or interchangeable to allow connection to other means of venous access (e.g. to a femoral vein catheter or jugular/subclavian vein catheter, central line, etc.) or to allow other gauges of needle to be fitted to allow for differences in vein sizes and to allow better comfort for the patient.

5.3.3 The access and return line needles shall contain a needle-stick protection device, e.g. one that conforms to the requirements of ISO 23908.

5.4 Needle stick protection device

Manufacturers shall give recommendations for the optimal use of the needle stick protection device.

NOTE Needle stick protection devices might be subjected to national requirements and standards.

5.5 Pre-collection sampling device

5.5.1 The pre-collection sampling device shall permit the collection, under aseptic conditions, of a range of donor samples.

5.5.2 If the pre-collection sampling device includes a pre-collection sampling bag, then its capacity shall be at least 25 ml.

5.5.3 The pre-collection sampling device shall be designed to be filled with a mean flow rate of at least 50 ml/min when tested in accordance with B.2.

5.5.4 Means shall be provided which prevent the return of blood and/or air from the sampling site towards the donor and donation after the filling of the pre-collection sampling device. The means may or may not be integrated. If the means is not integrated, the accompanying documents shall identify suitable means.

NOTE For collection of specific samples, it can be necessary to avoid the presence of anticoagulant and haemolysis in the pre-collection sample.

5.5.5 Manufacturers shall give recommendations for the optimal use of the pre-collection sampling device.

5.6 Red blood cell storage bag

5.6.1 Red blood cell storage bags shall allow the storage of packed red cells in a preservative red cell storage media (RAS) for up to 42 days when refrigerated between 2 °C and 6 °C or in accordance with national standards.

5.6.2 The manufacturer shall provide information regarding the suitability of the container for freezing (cryopreservation) of red cells in cryopreservation solution.

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5.7 Plasma storage bag

5.7.1 Plasma storage bags shall allow the storage of plasma for 2 years when refrigerated at below -25 °C.

5.7.2 The manufacturer shall provide information regarding the suitability of the container for freezing plasma.

5.8 Platelet storage bag

5.8.1 Platelet storage bags shall have good gas permeability for both oxygen and carbon dioxide and shall allow storage of platelet concentrates under temperature controlled conditions between 4 and 7 days (under continuous agitation).

5.8.2 Platelet storability is also influenced by the number of platelets, volume of platelet concentrate, size of the container and agitation, and is usually assessed by observation of swirling and by measurement of pH, hypotonic shock response, and aggregation.

5.9 Post-collection sampling device

5.9.1 Post-collection sampling device shall permit the collection, under aseptic conditions, of blood component samples into evacuated sample tubes.

5.9.2 If the post-collection sampling device includes a post collection sample container, the capacity of the container shall be at least 10 ml for bacterial control.

5.10 Collection and transfer tube(s)

5.10.1 The plastics container can be provided with one or more collection or transfer tube(s) to allow the collection of blood components and addition of red cell additive solution or platelet additive solution or transfer to another container, e.g. via a leucocyte filter.

5.10.2 If a transfer tube is present and if necessary to avoid unexpected flow between containers, it shall be fitted with a device which when loosened or opened, permits the free flow of blood components in either direction. Examples include clamping devices and frangible couplers.

5.10.3 The tubes shall be such that they can be sealed hermetically and do not collapse under normal use.

5.10.4 There shall be no leakage at the junctions and the plastics container shall also conform to the requirements specified in 6.2.7.

5.10.5 Requirements for sterile connection of transfer tubing: Tubing design shall allow the efficient transfer of blood components between containers. Design should also allow the joining of tubes supplied by a single manufacturer or from different manufacturers using a sterile tube welding device. Typically, this is to enable the connection of leukocyte filters (LCF) or other required devices when these are not included in the set. Sterile tube welding devices join the two opposing ends of the tube while maintaining a sterile fluid pathway.

5.10.6 Manufacturers of sterile tube welding devices typically specify acceptable tube dimensions (external and/or internal diameter and wall thickness) for use on their equipment. Aphaeresis blood bag system manufacturers must specify in their product documentation, the material, internal and external diameter, and wall thickness of all their tubing to allow blood transfusion services to assess the suitability for tube welding.

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5.10.7 When a blood transfusion service wishes to weld tubing of different specifications, they should carry out a validation before proceeding. A protocol is provided in Annex B.5 as a minimum standard for such validations.

5.11 Outlet port(s)

5.11.1 The plastics container (except for any waste bag) shall be provided with one or more outlet ports for the administration of blood and blood components through a transfusion set. The port(s) which shall have a puncturable, non-resealable closure port septum placed (14 ± 2) mm from the top of the port shall allow connection of a transfusion set having a closure-piercing device in accordance with ISO 1135-4 without leakage on insertion or during conditions of use including emptying under pressure (see 6.2.8). Before the closure is pierced by the point of the closure-piercing device, the outlet port(s) shall be tightly occluded by the closure-piercing device. When used in accordance with manufacturer's instructions, the piercing device shall not damage the plastic film of the plastics container on insertion.

NOTE 1 For the dimensions of the closure-piercing device, see ISO 1135-4.

When designing the outlet port to ensure good compatibility with closure-piercing devices, manufacturers should avoid the use of tubing that is highly inflexible. Thin walled tubing (<1 mm) should also be avoided as this tends to twist and collapse on insertion.

5.11.2 Each outlet port shall be fitted with a hermetically sealed, tamper-evident protector to maintain the sterility of the internal surface.

5.11.3 When tested in accordance with 6.2.8, the connection between the closure-piercing device and the blood component bag port shall show no evidence of leakage.

5.12 Suspension

The plastics containers provided on the set shall have adequate means of suspension or positioning (see, for example, eyelets in Figure 5) which do not interfere with the use of the plastics container during collection, storage, processing, transport, or administration. The means of suspending or positioning the container shall be capable of withstanding a tensile force of 20 N applied along the longitudinal axis of the outlet port(s) for 60 min at a temperature of (23 ± 2) °C without breaking.

6 Requirements

6.1 General

The plastics container shall be transparent, virtually colourless (see 6.2.4), flexible, sterile, non-pyrogenic, biologically safe (see 6.4), and non-breakable under conditions of use (see 6.2.5). It shall be compatible with the contents under normal conditions of storage. The plastics container shall meet the requirements for terminal sterilization and shall not become tacky during sterilization and storage for its shelf-life at temperatures not exceeding 40 °C.

The plastics container shall be stable biologically, chemically, and physically with respect to its contents during its shelf-life and shall not permit penetration of microorganisms. Any substances leached from the plastics container by the contained anticoagulant and/or preservative solution, blood, and blood components by either chemical interaction or physical dissolution, shall be within the limits specified.

In many countries, national pharmacopoeias specify formulations of different plastics materials such as flexible PVC with different plasticizers and other plastics materials while government regulations or standards can detail suitable tests for assessing chemical or physical interactions.

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6.2 Physical requirements

6.2.1 Conditions of manufacture

All processes involved in the manufacture, assembly, and storage of the plastics container shall be carried out under clean and hygienic conditions in compliance with the appropriate national regulations and in accordance with relevant legislation and international agreements such as current GMP requirements. Every practicable precaution shall be taken at all stages to reduce the risk of adventitious contamination by microorganisms or foreign matter.

6.2.2 Sterilization

6.2.2.1 The aphaeresis set shall have been sterilized by a validated method.

6.2.2.2 The method of sterilization used shall not adversely affect the materials or contents, nor cause any loosening of joints and deterioration of welds in the plastics material. The shape of the plastics container must meet the requirements of Table 1 after completion of the sterilization process.

6.2.2.3 The manufacturer shall be able to produce evidence acceptable to the national control authority of the effectiveness of the sterilization process actually used. If required by the national control authority, positive controls to check the effectiveness of sterilization shall be included in each sterilization lot.

6.2.3 Transparency

When tested as specified in B.1, the opalescence of the suspension shall be perceptible when viewed through the plastics container as compared with a similar plastics container filled with water.

6.2.4 Coloration

The material of the sterilized plastics container shall not be coloured to such an extent that assessment of the colour of the blood is adversely affected.

6.2.5 Thermal stability

This requirement refers to bags intended for freezing.

The plastics container filled to specified storage capacity with water for analytical laboratory use shall withstand a slow freezing to and storage at −80 °C for 24 h, subsequent immersion in water at (37 ± 2) °C for 60 min, and returning to (23 ± 2) °C. The plastics container shall meet the requirements of 5.10.3, 5.10.4, 5.12, 6.2.7, and 6.2.11.

6.2.6 Water vapour transmission for plastics containers prefilled with storage solution or anticoagulant

The plastics container, without an over-package, shall be filled to its nominal capacity with water as specified in ISO 3696, sealed and labelled ready for use. The plastics container shall then be capable of being stored for 42 days at a temperature of (4 ± 2) °C without loss of a mass fraction of more than 2 % of water from the solution.

NOTE The storage of certain blood components, such as platelet concentrates, can require specific gas exchange rates for oxygen and carbon dioxide.

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6.2.7 Resistance to leakage

6.2.7.1 Bags intended for centrifugation

Where the manufacturer specifies that the plastics container is suitable for centrifugation, the tests of this subclause are applicable.

When filled to specified storage capacity with water for analytical laboratory use and sealed, the plastics container shall not develop leaks under conditions of centrifugation at 5 000 g at (37 ± 2) °C for 10 min. The plastics container is then squeezed between two plates to an internal pressure equivalent to 40 kPa above atmospheric pressure at a temperature of (23 ± 2) °C for 10 min. No leakage is allowed on visual inspection.

For containers of flexible poly vinyl chloride (PVC), both tests should be repeated at (4 ± 2) °C. Plastics containers that are normally centrifuged without solution shall be subjected to the same centrifugation conditions as noted above without solution. Following this, the plastics container shall withstand an internal pressure equivalent to 40 kPa above atmospheric pressure after filling to nominal capacity.

6.2.7.2 Bags not intended for centrifugation

Where the manufacturer specifies that the plastics containers are not intended to be centrifuged, the tests of this subclause are applicable.

When filled to specified storage capacity with water for analytical laboratory use and sealed, the plastics container is then squeezed between two plates to an internal pressure equivalent to 40 kPa above atmospheric pressure at a temperature of (23 ± 2) °C for 10 min. No leakage is allowed on visual inspection.

NOTE 1 This test is used to verify that the seals of the bag are robust.

NOTE 2 When the plastics container is filled with anticoagulant solution, such as an ACD solution or other solutions with similar pH, leakage can be detected by pressing the plastics container against sheets of blue litmus paper and observing the development of pink spots on the paper. For solutions of other pH, the same method with an appropriate indicator can be used. Alternative methods affording at least the same degree of sensitivity can be used.

6.2.8 Insertion force

It shall be possible to puncture the output port septum of the blood component bag with a closure piercing device that meets the requirements of ISO 1135-4.

Published work indicates that insertion forces under specified conditions should be considered (see References [3] and [4]).

6.2.9 Pull force

When a closure-piercing device conforming to ISO 1135-4 is inserted into the blood component bag port, this shall resist a pull force of 15 N for 15 s.

6.2.10 Leakage after closure piercing

Fill the plastics container with a volume of water at a temperature of (23 ± 2) °C equal to its specified storage capacity. After puncturing the septum of the containers as described in 6.2.8, each test closure-piercing device shall remain in the septum point for 5 h. Then, place the plastics containers between two plane parallel plates loaded with an internal pressure of 20 kPa for 15 s and inspect for any leakage.

6.2.11 Particulate contamination

Plastics containers shall be manufactured so that contamination with particles is minimised.

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When tested as described in B.4, the fluid path within the plastics container should be free from visible particles.

NOTE Limits and test procedures given in pharmacopoeias, for example, those specified in the European Pharmacopoeia for parenteral solutions, can be applied for the aphaeresis blood bag system. Similar devices with the same intended use can be another source of consideration for particle size ranges and particle count limits.

6.3 Chemical requirements

6.3.1 Requirements for the raw container or sheeting

The sheeting shall fulfil the requirements given in the relevant pharmacopoeias. Alternatively, it can be tested as described in Table 2.

Table 2 — Ignition residues for polyolefins and PVC

Test	Plastics material	Maximum permissible residue	Test as specified in
Residue on ignition	Polyolefins	0,5 mg/g	A.2
	PVC containing plasticizers	1 mg/g	

6.3.2 Requirements for the test fluid

The limits specified in Table 3 shall not be exceeded when the appropriate tests are carried out on the extract obtained in accordance with Annex A.

Table 3 — Chemical limits on extracts from plastics container

Characteristics	Maximum permissible value	Test method in
Oxidizable constituents	1,5 ml	A.4.1
Ammonia	0,8 mg/l	A.4.2
Chloride ions (Cl^-)	4 mg/l	A.4.3
Metals: Ba, Cr, Cu, Pb Sn, Cd Al	For each metal: 1 mg/l For each metal: 0,1 mg/l 0,05 mg/l	A.4.4.1
Heavy metals	2 mg/l	A.4.4.2
Acidity or alkalinity	0,4 ml sodium hydroxide solution, c(NaOH) = 0,01 mol/l, or 0,8 ml hydrochloric acid, c(HCl) = 0,01 mol/l	A.4.5
Residue on evaporation	5 mg or 50 mg/l	A.4.6
Opalescence	Slightly opalescent, but not more pronounced than that of reference suspension	A.4.7
Coloration	No coloration	A.4.8
UV absorbance	In the range of 230 nm to 360 nm 0,25 for plastics containers with a nominal capacity ≤ 100 ml and 0,2 for plastics containers with a nominal capacity > 100 ml	A.4.9
Extractable plasticizer, e.g. di(2-ethylhexyl) phthalate (DEHP)[a]	15 mg/100 ml	A.4.10

[a] Only for flexible PVC containing DEHP.

Materials used in the manufacture of plastics containers for human blood and blood components shall be carefully chosen so as to minimize the risks arising from leaching of chemical constituents into

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the product. Particular attention shall be given to the toxicity of the materials used and the biological compatibility of the plastics container with the product.

NOTE National pharmacopoeias have monographs on plastic materials which specify the composition and limit of different constituents, as well as limits of metals such as Ba, Pb, Cd, Sn, Cr, and, for example, vinyl chloride monomers, where applicable.

6.4 Biological requirements

6.4.1 General

The plastics container shall not adversely affect the therapeutic effectiveness of blood and blood components and not release substances which can exhibit undue toxic, cytotoxic, bacteriostatic, bactericidal, pyrogenic, or haemolytic reactions.

Typical biological safety tests are given in the ISO 10993 series.

6.4.2 Impermeability for microorganisms

The plastics container shall be impermeable to microorganisms when tested as specified in C.3.

6.4.3 Compatibility

When tested as specified in C.4, C.5, and C.6, the plastics containers shall not release to the anticoagulant/preservative solution and/or blood or blood components any substances in such quantities that they have a pyrogenic, toxic, or haemolytic effect.

7 Packaging

7.1 General

The requirements in 7.2 to 7.6 are related to the plastics container in its sealed over-package.

7.2 Shelf-life

The shelf-life of the plastics container shall be established by the manufacturer on the basis of stability data. When containing anticoagulant and/or preservative solution, the container shall have a shelf-life not greater than the time during which the water loss from the container equals a mass fraction of 5 % at defined storage conditions of temperature and humidity when conditioned in accordance with ICHQ1 (R2) for the relevant climatic zones.

7.3 Over-package materials

The materials of the over-package or any treatment to its interior surface should neither interact with the plastic of the container or its contents nor support mould growth. If chemical fungicides are used, evidence shall be provided to show there has been no harmful penetration of or effect on the plastics container and its contents.

7.4 Over-package sealing

Where the over-package forms a sterile barrier, the over-package shall be sealed in such a manner as to be tamper-evident and to prevent opening or reclosing without displaying signs that the seal has been destroyed.

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7.5 Over-package strength

The over-package shall be strong enough to protect the product under conditions of normal handling and use.

7.6 Arrangement of components in the over-package

The plastics container and components shall be arranged in the over-package in a manner which will minimise the access and return lines or other tubing essential for performance and safety from kinking and acquiring a permanent set.

8 Labelling

8.1 General

The labelling of a plastics container shall include the requirements as specified in 8.2 to 8.5. If graphical symbols are used, refer to ISO 3826-2 and ISO 15223-1.

8.2 Label on plastics containers

With the exception of sample containers, the following information shall be included on the container label:

a) the name and address of the manufacturer;

b) nature, and volume (in millilitres) or mass (in grams) and formulation of anticoagulant and/or preservative solution incorporated in the container (if applicable);

c) catalogue number;

d) lot designation;

e) expiry date, if required.

NOTE All items can be included additionally in a bar code conforming to a 128 code.

8.3 Label on over-package

The over-package label shall contain:

a) the name and address of the manufacturer;

b) description of the contents;

c) catalogue number;

d) lot designation;

e) expiry date;

f) instruction or symbol that the container is for single use only;

g) statement or symbol defining the conditions of sterility and non-pyrogenicity;

h) any special conditions for storage of the package;

i) reference to the package insert or instructions for use for the aphaeresis set;

j) applicable special environmental and storage conditions (particularly for sets with incorporated solutions); and

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k) instruction or symbol indicating not to use the plastics container if there is any visible sign of deterioration.

If a transparent over-package is used, all the information required under 8.2 and 8.3 should appear on the label of the plastics container or the package insert or instructions for use.

NOTE Items a) through e) can be included additionally in a bar code conforming to a 128 code.

8.4 Package insert or instructions for use

The package insert shall contain:

a) the name and address of the manufacturer;

b) description of the contents;

c) formulation of any solutions incorporated in the set;

d) catalogue number;

e) definition of the storage conditions for the sets;

f) statement whether the container can be centrifuged;

g) intended use;

h) explanation of all symbols used on the shipping box, over-package, and bag labels if required;

NOTE Symbol definitions might not be required for symbols according ISO 15223-1.

i) necessary instructions for proper use of the set (if applicable); and

j) instruction indicating that the plastics container shall not be used more than n[3] days after removal from the over-package.

NOTE It is permissible to provide the instructions for use on the over-package label rather than on a package insert.

8.5 Label on shipping box

The label, which should be visible when paletted, shall contain:

a) the name and address of the manufacturer;

b) description of the contents;

c) model or catalogue number;

d) lot designation;

e) expiry date;

f) applicable special environmental and storage conditions (particularly for sets with incorporated solutions); and

g) if the transit container functions as an over-package, an instruction indicating that the plastics container shall not be used more than n[4] days after removal from the over-package.

NOTE Items c) through e) can be included additionally in a bar code conforming to a 128 code.

3) If there are no applicable national regulations, n is determined by the manufacturer.

4) If there are no applicable national regulations, n is determined by the manufacturer.

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8.6 Label requirements

The label on the plastics container shall be such that:

a) an appropriate label area is reserved for information related to the plastics container manufacturer and user;

NOTE Usually, 30 % of the label area is intended for entries of the manufacturer and 70 % of the label area is intended for entries or over-labelling of those who fill the plastics container with blood or blood components.

b) by leaving a portion of the plastics container visible and free of markings, the contents can be adequately inspected visually;

c) there is no diffusion of the print from the label into the material of the plastics container;

d) the printing on the label remains legible at the time of use;

e) any adhesive used on the label shall not support mould growth or migration of mould or chemicals from the adhesive through the bag into the contents of the bag. Evidence shall be provided to show there has been no harmful effect on the plastics container and its contents;

f) any attempt to peel off the label shall result in the label being destroyed;

g) when tested in accordance with B.3, the label(s) shall not separate from the plastics containers after removal from water. Printing on the label or on the plastics container shall remain legible.

9 Anticoagulant and/or preservative solution

The quality of the anticoagulant and/or preservative solution, if any, shall satisfy the requirements of the national pharmacopoeia and national regulations.

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Annex A
(normative)

Chemical tests

A.1 General

Take materials for testing from the blood and blood derivatives contact materials of the finished, sterilized, and if necessary, emptied plastics containers, i.e. in the state in which they would be used for transfusion, collection, separation, and administration procedures including the plastic sheet used for the collecting bag and the plastic tubing used for the collection tube, transfer tube, and any parts that come into contact with blood and blood components.

A.2 Determination of residue on ignition

Weigh 1,00 g to 2,00 g of the material (in small pieces) into a suitable crucible that has been previously ignited, cooled, and weighed. Heat at 100 °C to 105 °C for 1 h, then ignite to (550 ± 25) °C. Allow to cool in a desiccator and weigh. Repeat ignition until constant mass is attained. Calculate mass of residue on ignition per gram of starting material.

Equivalent methods as described in pharmacopoeias can be used.

A.3 Preparation of the test fluid

Fill the empty container twice to the nominal capacity with water for injection, shake for approximately 1 min, and then empty. After the rinse water has drained off, fill the empty container to the nominal volume with water for injection, then compress the container so that the remaining air escapes from the container, and subsequently close it. Extract the container for at least 30 min in pressurized, saturated steam at (121 ± 2) °C. Use 250 ml water for injection as a comparative fluid (blank sample). Heating and cooling times are not included in the 30 min cycle time requirement.

If appropriate, the extraction can be performed on pieces of sheeting or raw container. Use pieces with a total surface area of 1 500 cm^2 which includes both sides of the plastic sheet. Wash this material twice with 100 ml water for injection and discard the water after use. Drain the pieces, cover them with 250 ml water for injection, and extract for 30 min in pressurized, saturated steam at (121 ± 2) °C. As a comparison fluid (blank sample), treat water for injection in the same manner.

Test on pieces of sheeting are only possible if the plastics material is homogeneous. Laminated sheeting must be transformed into an equivalent container first to selectively test the inner surface.

If the container is not intended for sterilization at temperatures of at least 121 °C, then the extraction can alternatively be performed at (100 ± 2) °C for a duration of 2 h or at (70 ± 2) °C for a duration of (24 ± 2) h, in which case, the selected temperature should not be lower than that at which the container is being sterilized.

In the event that the solution resulting from extraction of a single container or single sample of sheeting has insufficient volume to allow for all of the required testing, the solutions from two or more extractions can be combined to produce a composite test solution. If alternative sterilization methods other than thermal sterilization are to be applied to the container, e.g. γ-irradiation, ethylene oxide, or e-beam, use sterilized containers for preparation of the test fluid.

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A.4 Tests

A.4.1 Determination of oxidizable constituents

Boil for 3 min 20,0 ml of the test fluid with 20,0 ml potassium permanganate solution [$c(KMnO_4)$ = 0,002 mol/l] and 1,0 ml sulfuric acid [$c(H_2SO_4)$ = 1 mol/l]. Add 1,0 g of potassium iodide and titrate the solution with sodium thiosulfate solution [$c(Na_2S_2O_3)$ = 0,01 mol/l] until light-brown. Then add five drops of starch solution and titrate until colourless.

Calculate the consumption of potassium permanganate solution [$c(KMnO_4)$ = 0,01 mol/l] for the test fluid and water serving as comparison fluid. The difference between the two values shall not be greater than 1,5 ml.

A.4.2 Determination of ammonia

Make alkaline 10 ml of the test fluid by the addition of 2 ml of caustic soda [c(NaOH) = 1 mol/l], dilute with distilled water to 15 ml, and then add 0,3 ml Nessler's reagent[5] .

Prepare the comparison solution simultaneously by making alkaline 8 ml of ammonium standard solution [$\rho(NH_4^+)$ = 1 mg/l] by the addition of 2 ml caustic soda [c(NaOH) = 1 mol/l], diluting with distilled water to 15 ml and then adding 0,3 ml Nessler's reagent.

After 30 s, examine the solution which shall not be more strongly yellow-coloured than the comparison solution.

A.4.3 Determination of chloride ions

Add 0,3 ml of silver nitrate solution [$c(AgNO_3)$ = 0,1 mol/l] to 0,15 ml of diluted nitric acid. Add the resultant solution to 15 ml of the extract.

Prepare a reference solution in the same way using 12 ml of chloride standard solution (5 mg Cl^- per litre) and 3 ml of water.

Shake the mixtures. After 2 min, the solution prepared by using the extract shall not be more turbid than the reference solution. Avoid exposure of the solution to direct daylight.

A.4.4 Determination of metals

A.4.4.1 Heavy metals related to Pb^{2+}

The metals Ba, Cd, Cr, Cu, Pb, Sn, and Al are determined by atomic spectrometric analysis. The detection limit using Atomic Absorption Spectrometry (AAS) can be raised by concentrating the test fluid by evaporation in accordance with A.3, in which case, 2,5 ml hydrochloric acid solution [ρ(HCl) = 10 g/l] is added to 250 ml test fluid.

A.4.4.2 Alternative methods for testing for heavy metals

Chemical determination of the total of heavy metals can be used instead of the atomic spectrometric determination of metals in the test fluid according to A.3.

1,2 ml thioacetamide reagent is added to 12 ml of the test fluid and 2 ml ammonium acetate buffer solution (pH = 3,5) and immediately mixed.

Prepare the comparison solution in the same manner using 10 ml lead solution [$\rho(Pb^{2+})$ = 2 mg/l] and adding 2 ml of the test fluid. After 2 min, examine the solution. It shall not be a deeper shade of brown than the comparison solution.

5) See, for example, *European Pharmacopoeia.*

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A.4.5 Determination of acidity or alkalinity

After the addition of 2 drops of phenolphthalein solution, 10 ml of the test fluid shall not be coloured red. However, on the addition of less than 0,4 ml caustic soda [c(NaOH) = 0,01 mol/l], red coloration shall occur. After the addition of 0,8 ml hydrochloric acid [c(HCl) = 0,01 mol/l], this coloration shall disappear again. On the addition of 5 drops methyl red solution, the solution shall have an orange-red coloration.

A.4.6 Determination of the evaporation residue

Evaporate 100 ml of the test fluid on a water bath and dry at 105 °C to constant mass.

A.4.7 Determination of turbidity and degree of opalescence

A.4.7.1 General

Using identical test tubes of colourless, transparent, neutral glass with a flat base and an internal diameter of 15 mm to 25 mm, compare the liquid to be examined with a reference suspension freshly prepared as described below the depth of the layer being 40 mm. Compare the solutions in diffused daylight 5 min after preparation of the reference suspension viewing them vertically against a black background. The diffusion of light shall be such that reference suspension 1 can readily be distinguished from water and that reference suspension 2 can readily be distinguished from reference suspension 1.

A.4.7.2 Reagents

A.4.7.2.1 Hydrazine sulfate solution

Dissolve 1 g of hydrazine sulfate in water and dilute to 100 ml. Allow to stand for 4 h to 6 h.

A.4.7.2.2 Hexamethylenetetramine solution

Dissolve 2,5 g of hexamethylenetetramine in 25 ml of water in a 100 ml glass-stoppered flask.

A.4.7.2.3 Primary opalescent suspension

Add to the solution of hexamethylenetetramine (A.4.7.2.2) 25 ml of the hydrazine sulfate solution (A.4.7.2.1). Mix and allow to stand for 24 h.

This suspension is stable for two months provided that it is stored in a glass container free from surface defects. The suspension shall not adhere to the glass and shall be well-mixed before use.

A.4.7.2.4 Standard of opalescence

Dilute 15 ml of the primary opalescent suspension (A.4.7.2.3) to 1 000 ml with water.

This suspension shall be freshly prepared and can be stored for at most 24 h.

A.4.7.2.5 Reference suspensions

Prepare the reference suspensions in accordance with Table A.1. Mix and shake before use.

Table A.1 — Reference suspensions

Volumes in millilitres

Reference suspension	**1**	**2**	**3**	**4**
Standard of opalescence, volume	5	10	30	50
Water, volume	95	90	70	50

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A.4.7.3 Expression of results

A.4.7.3.1 A liquid is deemed to be *clear* if its clarity is the same as that of water or of the solvent used when examined under the conditions described above or if its opalescence is not more pronounced than that of reference suspension 1.

A.4.7.3.2 A liquid is deemed to be *slightly opalescent* if its opalescence is more pronounced than as described in A.4.7.3.1, but not more pronounced than that of reference suspension 2.

A.4.7.3.3 A liquid is deemed to be *opalescent* if its opalescence is more pronounced than as described in A.4.7.3.2, but not more pronounced than that of reference suspension 3.

A.4.7.3.4 A liquid is *highly opalescent* if its opalescence is more pronounced than as described in A.4.7.3.3, but not more pronounced than that of reference suspension 4.

A.4.8 Determination of degree of coloration

A.4.8.1 General

The examination of the degree of coloration of liquids in the range brown-yellow-red shall be carried out by one of the two methods specified in A.4.8.2 and A.4.8.3.

A.4.8.2 Method 1

Using matched tubes of colourless, transparent, neutral glass having an internal diameter of 12 mm, compare 2 ml of the liquid to be examined with 2 ml of water. Compare the colours in diffused daylight viewing them horizontally against a white background.

A.4.8.3 Method 2

Using matched tubes of colourless, transparent, neutral glass having an internal diameter of 16 mm, compare 10 ml of the liquid to be examined with 10 ml of water. Examine the column of liquid down the vertical axis of the tube in diffused daylight against a white background.

A.4.8.4 Expression of results

A liquid is deemed to be colourless if it has the appearance of water when examined under the conditions as specified for method 1 or 2.

A.4.9 Determination of the UV absorption

Determine the UV absorbance of the extract in a cuvette with an internal light path of 1 cm against the blank. The absorbance is determined in the range from 230 nm to 360 nm.

A.4.10 Determination of plasticizer as extractable di(2-ethylhexyl) phthalate (DEHP)

NOTE This determination applies only to flexible PVC containing DEHP.

A.4.10.1 Reagents

A.4.10.1.1 Ethanol, volume fraction, φ, in the range from 95,1 % to 96,6 %, density, ρ, in the range from 0,805 0 g/ml to 0,812 3 g/ml.

A.4.10.1.2 Extraction solvent, ethanol:water mixture of density, ρ, ranging from 0,937 3 g/ml to 0,937 8 g/ml as determined with a pycnometer.

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