3.2.3. Sterile plastic containers for human blood

DEFINITION
Plastic containers for aqueous solutions for parenteral infusion are manufactured from one or more polymers, if necessary with additives. The containers described in this section are not necessarily suitable for emulsions. The polymers most commonly used are polyethylene, polypropylene and poly(vinyl chloride). The specifications of this text are to be read in conjunction with section 3.2.2. Plastic containers and closures for pharmaceutical use.

The containers may be bags or bottles. They have a site suitable for the attachment of an infusion set designed to ensure a secure connection. They may have a site that allows an injection to be made at the time of use. They usually have a part that allows them to be suspended and which will withstand the tension occurring during use. The containers must withstand the sterilisation conditions to which they will be submitted. The design of the container and the method of sterilisation chosen are such that all parts of the containers that may be in contact with the infusion are sterilised. The containers are impermeable to micro-organisms after closure. The containers are such that after filling they are resistant to damage from accidental freezing which may occur during transport of the final preparation. The containers are and remain sufficiently transparent to allow the appearance of the contents to be examined at any time, unless otherwise justified and authorised. The empty containers display no defects that may lead to leakage and the filled and closed containers show no leakage. For satisfactory storage of some preparations, the container has to be enclosed in a protective envelope. The initial evaluation of storage has then to be carried out using the container enclosed in the envelope.

TESTS
Solution S. Use solution S within 4 h of preparation. Fill a container to its nominal capacity with water R and close it, if possible using the usual means of closure; otherwise close using a sheet of pure aluminium. Heat in an autoclave so that a temperature of 121 ± 2 °C is reached within 20 min to 30 min and maintain at this temperature for 30 min. If heating at 121 °C leads to deterioration of the container, heat at 100 °C for 2 h. Blank. Prepare a blank by heating water R in a borosilicate-glass flask closed by a sheet of pure aluminium at the temperature and for the time used for the preparation of solution S.

Appearance of solution S. Solution S is clear (2.2.1) and colourless (2.2.2, Method II).

Acidity or alkalinity. To a volume of solution S corresponding to 4 per cent of the nominal capacity of the container add 0.1 ml of phenolphthalein solution R. The solution is colourless. Add 0.4 ml of 0.01 M sodium hydroxide. The solution is pink. Add 0.8 ml of 0.01 M hydrochloric acid and 0.1 ml of methyl red solution R. The solution is orange-red or red.

Absorbance (2.2.25). Measure the absorbance of solution S from 230 nm to 360 nm, using the blank (see solution S) as the compensation liquid. At these wavelengths, the absorbance is not greater than 0.20.

Reducing substances. To 20.0 ml of solution S add 1 ml of dilute sulphuric acid R and 20.0 ml of 0.002 M potassium permanganate. Boil for 3 min. Cool immediately. Add 1 g of potassium iodide R and titrate immediately with 0.01 M sodium thiosulphate, using 0.25 ml of starch solution R as indicator. Carry out a titration using 20.0 ml of the blank. The difference between the titration volumes is not greater than 1.5 ml.

Transparency. Fill a container previously used for the preparation of solution S with a volume equal to the nominal capacity of the primary opalescent suspension (2.2.1) diluted 1 in 200 for a container made from polyethylene or polypropylene and 1 in 400 for other containers. The opaqueness of the suspension is perceptible when viewed through the container and compared with a similar container filled with water R.

LABELLING
The label accompanying a batch of empty containers includes a statement of:
– the name and address of the manufacturer,
– a batch number which enables the history of the container and of the plastic material of which it is manufactured to be traced.

3.2.3. STERILE PLASTIC CONTAINERS FOR HUMAN BLOOD AND BLOOD COMPONENTS
Plastic containers for the collection, storage, processing and administration of blood and its components are manufactured from one or more polymers, if necessary with additives. The composition and the conditions of manufacture of the containers are registered by the relevant national authorities in accordance with the relevant national legislation and international agreements. When the composition of the materials of the different parts of the containers correspond to the appropriate specifications, their quality is controlled by the methods indicated in those specifications (see 3.1. Materials used for the manufacture of containers and subsections).

Materials other than those described in the Pharmacopoeia may be used provided that their composition is authorised by the competent authority and that the containers...
manufactured from them comply with the requirements prescribed for Sterile Plastic Containers for Human Blood and Blood Components.

In normal conditions of use the materials do not release monomers, or other substances, in amounts likely to be harmful nor do they lead to any abnormal modifications of the blood.

The containers may contain anticoagulant solutions, depending on their intended use, and are supplied sterile.

Each container is fitted with attachments suitable for the intended use. The container may be in the form of a single unit or the collecting container may be connected by one or more tubes to one or more secondary containers to allow separation of the blood components to be effected within a closed system.

The outlets are of a shape and size allowing for adequate connection of the container with the blood-giving equipment. The protective coverings on the blood-taking needle and on the appendages must be such as to ensure the maintenance of sterility. They must be easily removable but must be tamper-proof.

The capacity of the container is related to the nominal capacity prescribed by the national authorities and to the appropriate volume of anticoagulant solution. The nominal capacity is the volume of blood to be collected in the container. The containers are of a shape such that when filled they may be centrifuged.

The containers are fitted with a suitable device for suspending or fixing which does not hinder the collection, storage, processing or administration of the blood.

The containers are enclosed in sealed, protective envelopes.

CHARACTERS

The container is sufficiently transparent to allow adequate visual examination of its contents before and after the taking of the blood and is sufficiently flexible to offer minimum resistance during filling and emptying under normal conditions of use. The container contains not more than 5 ml of air.

TESTS

Solution S1. Fill the container with 100 ml of a sterile, pyrogen-free 9 g/1 solution of sodium chloride R. Close the container and heat it in an autoclave so that the contents are maintained at 110 °C for 30 min.

If the container to be examined contains an anticoagulant solution, first empty it, rinse the container with 250 ml of water for injections R at 20 ± 1 °C and discard the rinsings.

Solution S2. Introduce into the container a volume of water for injections R corresponding to the intended volume of anticoagulant solution. Close the container and heat it in an autoclave so that the contents are maintained at 110 °C for 30 min. After cooling, add sufficient water for injections R to fill the container to its nominal capacity.

If the container to be examined contains an anticoagulant solution, first empty it and rinse as indicated above.

Resistance to centrifugation. Introduce into the container a volume of water R, acidified by the addition of 1 ml of dilute hydrochloric acid R, sufficient to fill it to its nominal capacity. Envelop the container with absorbent paper impregnated with a 1 in 5 dilution of bromophenol blue solution R1 or other suitable indicator and then dried. Centrifuge at 5000 g for 10 min. No leakage perceptible on the indicator paper and no permanent distortion occur.

Resistance to stretch. Introduce into the container a volume of water R, acidified by the addition of 1 ml of dilute hydrochloric acid R, sufficient to fill it to its nominal capacity. Suspend the container by the suspending device at the opposite end from the blood-taking tube and apply along the axis of this tube an immediate force of 20 N (2.05 kgf). Maintain the traction for 5 s. Repeat the test with the force applied to each of the parts for filling and emptying. No break and no deterioration occur.

Leakage. Place the container which has been submitted to the stretch test between two plates covered with absorbent paper impregnated with a 1 in 5 dilution of bromophenol blue solution R1 or other suitable indicator and then dried. Progressively apply force to the plates to press the container so that its internal pressure (i.e. the difference between the applied pressure and atmospheric pressure) reaches 67 kPa within 1 min. Maintain the pressure for 10 min. No signs of leakage are detectable on the indicator paper or at any point of attachment (seals, joints, etc.).

Vapour permeability. For a container containing an anticoagulant solution, fill with a volume of 0.9 g/1 solution of sodium chloride R equal to the volume of blood for which the container is intended.

For an empty container, fill with the same mixture of anticoagulant solution and sodium chloride solution. Close the container, weigh it and store it at 5 ± 1 °C in an atmosphere with a relative humidity of (50 ± 5) per cent for 21 days. At the end of this period the loss in mass is not greater than 1 per cent.

Emptying under pressure. Fill the container with a volume of water R at 5 ± 1 °C equal to the nominal capacity. Attach a transfusion set without an intravenous cannula to one of the connectors. Compress the container so as to maintain throughout the emptying an internal pressure (i.e. the difference between the applied pressure and atmospheric pressure) of 40 kPa. The container empties in less than 2 min.

Speed of filling. Attach the container by means of the blood-taking tube fitted with the needle to a reservoir containing a suitable solution having a viscosity equal to that of blood, such as a 335 g/l solution of sucrose R at 37 °C. Maintain the internal pressure of the reservoir (i.e. the difference between the applied pressure and atmospheric pressure) at 9.3 kPa with the base of the reservoir and the upper part of the container at the same level. The volume of liquid which flows into the container in 8 min is not less than the nominal capacity of the container.

Resistance to temperature variations. Place the container in a suitable chamber having an initial temperature of 20 °C to 23 °C. Cool it rapidly in a deep-freeze to −80 °C and maintain it at this temperature for 24 h. Raise the temperature to 50 °C and maintain for 12 h. Allow to cool to room temperature. The container complies with the tests for resistance to centrifugation, resistance to stretch, leakage, vapour permeability emptying under pressure and speed of filling prescribed above.

Transparency. Fill the empty container with a volume equal to its nominal capacity of the primary opalescent suspension (2.2.1) diluted so as to have an absorbance (2.2.25) at 640 nm of 0.37 to 0.43 (dilution factor about 1 in 16). The cloudiness of the suspension must be perceptible when viewed through the bag, as compared with a similar container filled with water R.
**Extractable matter.** Tests are carried out by methods designed to simulate as far as possible the conditions of contact between the container and its contents which occur in conditions of use.

The conditions of contact and the tests to be carried out on the eluates are prescribed, according to the nature of the constituent materials, in the particular requirements for each type of container.

**Haemolytic effects in buffered systems**

**Stock buffer solution.** Dissolve 90.0 g of sodium chloride R, 34.6 g of disodium hydrogen phosphate R and 2.43 g of sodium dihydrogen phosphate R in water R and dilute to 1000 ml with the same solvent.

**Buffer solution A.** To 30.0 ml of stock buffer solution add 10.0 ml of water R.

**Buffer solution B.** To 30.0 ml of stock buffer solution add 20.0 ml of water R.

**Buffer solution C.** To 15.0 ml of stock buffer solution add 85.0 ml of water R.

Introduce 1.4 ml of solution S₂ into each of three centrifuge tubes. To tube I add 0.1 ml of buffer solution A₀₂, to tube II 0.1 ml of buffer solution B₀₂ and to tube III add 0.1 ml of buffer solution C₀₂. To each tube add 0.02 ml of fresh, heparinised human blood, mix well and warm on a water-bath at 30 ± 1 °C for 40 min. Use blood collected less than 3 h previously or blood collected into an anticoagulant citrate-phosphate-dextrose solution (CPD) less than 24 h previously.

Prepare three solutions containing, respectively:

- 3.0 ml of buffer solution A₀ (solution A₁),
- 4.0 ml of buffer solution B₀ (solution B₁),
- 4.75 ml of buffer solution B₀, and 10.25 ml of water R (solution C₁).

To tubes I, II and III add, respectively, 1.5 ml of solution A₁, 1.5 ml of solution B₁, and 1.5 ml of solution C₁. At the same time and in the same manner, prepare three other tubes, replacing solution S₁ by water R. Centrifuge simultaneously the tubes to be examined and the control tubes at exactly 2500 g in the same horizontal centrifuge for 5 min. After centrifuging, measure the absorbances (2.2.25) of the liquids at 540 nm using the stock buffer solution as compensation liquid. Calculate the haemolytic value as a percentage from the expression:

\[ \frac{A_{\text{exp}}}{A_{\text{100}}} \times 100 \]

- \(A_{\text{100}}\) = absorbance of tube III,
- \(A_{\text{exp}}\) = absorbance of tube I or II or of the corresponding control tubes.

The solution in tube I gives a haemolytic value not greater than 10 per cent and the haemolytic value of the solution in tube II does not differ by more than 10 per cent from that of the corresponding control tube.

**Sterility (2.6.1).** The containers comply with the test for sterility. Introduce aseptically into the container 100 ml of a sterile 9 g/l solution of sodium chloride and shake the container to ensure that the internal surfaces have been entirely wetted. Filter the contents of the container through a membrane filter and place the membrane in the appropriate culture medium, as prescribed in the test for sterility.

**Pyrogens (2.6.8).** Solution S₁ complies with the test for pyrogens. Inject 10 ml of the solution per kilogram of the rabbit’s mass.

**Abnormal toxicity (2.6.9).** Solution S₁ complies with the test for abnormal toxicity. Inject 0.5 ml of the solution into each mouse.

**PACKAGING**

The containers are packed in protective envelopes. On removal from its protective envelope the container shows no leakage and no growth of micro-organisms. The protective envelope is sufficiently robust to withstand normal handling.

**LABELLING**

The labelling complies with the relevant national legislation and international agreements. The label states:

- the name and address of the manufacturer,
- a batch number which enables the history of the container and of the plastic material of which it is manufactured to be traced.

A part of the label is reserved for:
- the statement of the blood group, the reference number and all other information required by national legislation or international agreements, and an empty space is provided for the insertion of supplementary labelling.

The label of the protective envelope or the label on the container, visible through the envelope, states:

- the expiry date,
- that, once withdrawn from its protective envelope, the container must be used within 10 days.

The ink or other substance used to print the labels or the writing must not diffuse into the plastic material of the container and must remain legible up to the time of use.

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**3.2.4. EMPTY STERILE CONTAINERS OF PLASTICISED POLY(VINYL CHLORIDE) FOR HUMAN BLOOD AND BLOOD COMPONENTS**

Unless otherwise authorised as described under Sterile Plastic Containers for Human Blood and Blood Components (3.2.3), the nature and composition of the material from which the containers are made comply with the requirements for Materials based on Plasticised Poly(vinyl chloride) for Containers for Human Blood and Blood Components and for Containers for aqueous solutions for intravenous infusion (3.1.1).

**TESTS**

They comply with the tests prescribed for Sterile Plastic Containers for Human Blood and Blood Components (3.2.2) and with the following tests to detect extractable matter.

**Reference solution.** Heat water for injections R in a borosilicate-glass flask in an autoclave at 110 °C for 30 min.

**Oxidisable substances.** Immediately after preparation of solution S₁ (see 3.2.3), transfer to a borosilicate-glass flask a quantity corresponding to 8 per cent of the nominal capacity of the container. At the same time, prepare a blank using an equal volume of the freshly prepared reference solution in another borosilicate-glass flask. To each solution add