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6. PRIMARY PACKAGING FOR PHARMACEUTICALS
6.1. CONTAINERS

This chapter deals with the specific requirements, guidance and information on containers used for packaging of pharmaceutical products. The materials that are used in the manufacture of containers, particularly plastic containers, the raw materials and additives used and the formulations employed should be agreed with the users of the containers. Any changes should also be notified to the users from time to time to enable them to ensure the stability and safety of the drugs packed in the containers.

A container and its closure for Pharmacopoeial article is intended to contain a drug substance or drug product with which it is, or may be in direct contact.

Containers and their closures must be chosen with care and after taking into consideration the nature of the articles and the likely effects of transportation and storage, even for short periods of time.

A container and its closure should be designed so that the contents may be removed in a manner suitable for the intended use of the article in it. It should also provide an adequate degree of protection, minimise the loss of constituents and should not interact physically or chemically with the contents in a way that will alter their quality to an extent beyond the limits given in the individual monograph, or present a risk of toxicity.

The choice of a container and its closure for any article is also governed by the likely period of storage of the article during which its quality will not be compromised to a degree where it will be unfit for use. Under the heading Storage, the pharmacopoeia indicates the measures to be taken to protect the article from contamination and deterioration during its entire shelf-life. Specifications for the container to be used for any article have not been given but in certain cases, the type of container that is recommended is stated in terms that have the following meanings.

Airtight container. A container that is impermeable to solids, liquids and gases under ordinary conditions of handling, storage and transport. If the container is intended to be opened on more than once, it must be so designed that it remains airtight after re-closure.

Hermetically Sealed container. A container that is impervious to air or any other gas under normal conditions of handling, shipment, storage and distribution, e.g. sealed glass ampoule, gas cylinder etc.

Light-resistant container. A container that protects the contents from the effects of actinic light by virtue of the specific properties of the material of which it is made. Alternatively, a clear and colourless or a translucent container may be made light-resistant by means of an opaque (light-resistant) covering and/or stored in a dark place; in such cases, the label on the container should bear a statement that the opaque covering or storage in dark place is needed until the contents have been used up.

Multidose container. A container that holds a quantity of the preparation suitable for two or more doses.

Sealed container. A container closed by fusion of the material of the container.

Single-dose container. A container that holds a quantity of the preparation intended for total or partial use as a single administration.

Tamper-evident container. A container fitted with a device or mechanism that reveals irreversibly whether the container has been opened.

Tightly-closed container. A tightly-closed container protects the contents from contamination by extraneous liquids, solids or vapours, from loss or deterioration of the article from effervescence, deliquescence or evaporation under normal conditions of handling, shipment, storage and distribution. A tightly-closed container must be capable of being tightly re-closed after use. Where a tightly-closed container is specified, a hermetically sealed container may be used for a single dose of an article. A gas cylinder may be considered to be a metallic, tightly-closed container designed to hold gas under pressure.

Well-closed container. A well-closed container protects the contents from extraneous solids and liquids and from loss of the article under normal conditions of handling, shipment, storage and distribution.

6.1.1. Plastic Containers

The commonly used plastic resins conforming to Indian Standards for the manufacture of plastic container and closures are polyethylene terephthalate (PET) (IS 12252), polyethylene (IS 10146), polyvinyl chloride (IS 10151), polypropylene (IS 10910), cyclic olefins, polyamides [nylon 6 (IS 12247)], polycarbonate (IS 14971), poly (ethylenevinyl acetate) (IS 13601). However, if the manufacturer of pharmacopoeial articles intends to use plastics made from polymers other than listed above, it should be justified and authorised by appropriate competent authority.

The resin identification codes - in compliance with IS 14534 must be visibly marked on the plastic containers.
The plastic containers should be manufactured from materials that do not include in their composition any substances that can be extracted by any contents in such quantities so as to alter the efficacy or stability of the product or to present a toxic hazard. A summary of the manufacture and usage of plastic container and closures is provided in the Table 1.

### Table 1 - Overview of the Life Cycle of Plastic Materials for Pharmacopoeial Articles

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<td>Bottles, Tubes, Caps, Closures, Packaging Products Identification Codes: Code No.1 = PET Code No.2 = HDPE (High Density PE) Code No.3 = V (PVC, Polyvinyl Chloride) Code No.4 = LDPE (Low Density PE) Code No.5 = PP Code No.6 = PS (Polystyrene) Code No.7 = Other plastics</td>
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The selection of a suitable plastic container should be based on knowledge, obtained from the supplier of the raw materials used and of the composition of the plastic so that potential hazards can be assessed. The plastic container chosen for any particular product should be such that the ingredients of the product in contact with the plastic material are not significantly adsorbed on its surface and do not significantly migrate into or through the plastic. Type samples of the intended container should be packed with the product and tested under conditions that reproduce those that would be encountered in use. These tests should include examination of the product to ensure absence of any sensory, chemical or physical change, an assessment of changes in the quality of contents due to permeability of the plastic, detection of changes in pH, an assessment of the effects of light, chemical tests and where necessary, biological tests. Containers from bulk production should conform to the type sample in every respect. It should be ensured that there is no change in the composition or any change in the manufacturing method used by the manufacturer and more importantly, that no use is made of scrap material. It must be emphasized that changes in the composition of the plastic, reworking or inadequate control of processing can bring about changes which may invalidate the results of type testing. Samples from production should be tested to ensure conformance to type samples and test schedules should be designed to check departures from the characteristic of the type sample. The biological and chemical tests described below are intended for plastic containers in which pharmaceutical formulations are packaged. It should be appreciated that these tests by themselves are not sufficient to establish safety or suitability of the plastic containers for the preparations and it is necessary to consider the results of the tests in conjunction with the information given above. Specification should be agreed with the container manufacturer and should be revised if the composition of the plastic or the ingredient quality is altered or the processing treatment is changed.

**Biological Tests**

Applicability of the test.

- Containers closure systems used for oral and topical dosage forms do not need any biological test.
In vitro testing described in (2.2.23) is applicable to the container closure systems used for all dosage forms except for oral and topical dosage forms.

Container closure systems that meet the requirements of the in vitro tests are not required to undergo any further in vivo testing (2.2.24).

The container closure systems that do not meet the requirements of the in vitro tests where applicable are required to undergo further in vivo testing.

Container closure systems that do not meet the requirements of the biological reactivity tests [(2.2.23) and (2.2.24), if appropriate] are not suitable as container closure systems for pharmaceutical use.

### 6.1.1.1. Plastic Containers for Parenteral Preparations

#### General Requirements

**Material.** Plastic containers for parenteral preparations are manufactured from one or more polymers. The polymers most commonly used are polyethylene, polypropylene and poly vinyl chloride. Only virgin plastic material, which is practically odourless, is used in the manufacture of the containers. Additives such as antioxidants, lubricants, plasticisers, stabilisers, etc. may be used but no pigment may be used for purposes of colouring. Recycling of excess material of well-defined nature and proportions may be permitted after appropriate validation.

**Characteristics.** 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. Although it may not be feasible to include parameters for construction and design of containers in terms of size, shape and weight, for example those meant for large volume parenterals (LVP), of different materials and made on different machines, both manufactured indigenously and internationally, involved in the production of such plastic containers, nevertheless the integrity of neck and shoulders of the containers should be suitably and appropriately strengthened and it shall be the responsibility of such LVP manufacturers to ensure that the containers withstand the stress conditions and rigors of transportation and packaging. 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 sterile. 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 container shows no leakage.

For satisfactory closure of some preparations, the container should be enclosed in a protective envelope. The initial evaluation of storage is then to be carried out using the container enclosed in the envelope.

#### Tests on Containers

**Leakage test, Collapsibility test.** Comply with the tests described under Plastic Containers for Non-parenteral Preparations.

**Solution S.** Fill a container to its nominal capacity with water 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 to 30 minutes and maintain at this temperature for 30 minutes. If heating at 121°C leads to deterioration of the container, heat at 100°C for 2 hours.

*NOTE-* Use solution S within 4 hours of its preparation.

**Blank.** Prepare a blank by heating water 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.

**Clarity and colour of solution S.** Solution S is clear (2.4.1) and is colourless (2.4.1).

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

**Light absorption.** The light absorption in the range 230nm to 360nm of solution S using a blank prepared as described under Solution S is not more than 0.20 (2.4.7).

**Reducing substances.** To 20.0mL of solution S add 1mL of *dilute sulphuric acid* and 20.0mL of 0.002M potassium permanganate. Boil for 3 minutes. Cool immediately. Add 1g of potassium iodide and titrate immediately with 0.01M sodium thiosulphate, using 0.25mL of *starch solution* as indicator. Carry out a titration using 20.0mL of the blank prepared as described under Solution S. The difference between the titration volumes is not more than 1.5mL.
**Transparency.** Fill the container previously used for the preparation of solution S to its nominal capacity with a 1 in 200 dilution of the standard suspension (2.4.1) for a container made from polyethylene or polypropylene. For containers of other materials, use a 1 in 400 dilution. The cloudiness of the suspension is perceptible when viewed through the container and compared with a similar container filled with water (2.4.1).

**Labelling.** The label accompanying a batch of empty containers states (1) the name and address of the manufacturer; (2) a batch number which enables tracing the history of the container and of the plastic material of which it is manufactured.

**Tests on Container Material**

The following tests are done on portions of the container that are unlabelled, unprinted or non-laminated or on the granules of plastic in the case of containers made by the ‘form-fill-seal’ process.

**Barium.** Moisten 2g with hydrochloric acid and ignite in a platinum dish. Dissolve the residue in 10mL of 1M hydrochloric acid, filter and add 1mL of 1M sulphuric acid to the filtrate. Any turbidity produced is not greater than that produced on adding 1mL of 1M sulphuric acid to a mixture of 10mL barium standard solution (10ppm Ba) and 10mL of 1M hydrochloric acid.

**Heavy metals.** To 2.5g in a long-necked round-bottomed flask add 20mL of sulphuric acid and char for about 10 minutes. Add hydrogen peroxide solution (100 vol) dropwise to the hot solution until it becomes colourless, heating between each addition until white fumes are evolved. Cool, transfer to a platinum dish with the aid of 10mL of water and evaporate to dryness. Dissolve the residue in 10mL of 1M hydrochloric acid, filter if necessary and add sufficient water to produce 25mL (solution A).

To a mixture of 10mL of solution A and 2mL of acetate buffer pH 3.5 add 1.2mL of thioacetamide reagent, mix immediately and allow to stand for 2 minutes. Any yellow colour in the solution is not more intense than the yellow colour obtained by repeating the operation using 10mL of cadmium standard solution (10ppm Cd) in place of solution A. Any brown colour in the solution is not more intense than that obtained by repeating the operation using a mixture of 5mL of lead standard solution (10ppm Pb) and 5mL of water in place of solution A.

**Tin.** To 10mL of solution A obtained in the test for Heavy metals add 5mL of sulphuric acid (20%), 1mL of a 1% w/v solution of sodium dodecyl sulphate and 1mL of zinc dithiol reagent. Heat in a water-bath for exactly 1 minute, cool and allow to stand for 30 minutes. Any red colour in the solution is not more intense than the red colour obtained by repeating the operation using 10mL of tin standard solution (5ppm Sn) in place of solution A.

**Zinc.** To 1mL of solution A obtained in the test for Heavy metals add sufficient water to produce 100mL. To 10mL of the resulting solution (test solution) add 5mL of acetate buffer solution pH 4.4, 1mL of 0.1M sodium thiosulphate and 5mL of 0.001% w/v solution of dithizone in chloroform, shake and allow to stand for 2 minutes. Any violet colour in the chloroform layer is not more intense than that obtained by repeating the operation using a mixture of 2 mL of zinc standard solution (10ppm Zn) and 8mL of water in place of the test solution. Carry out a blank determination using 10mL of water in place of test solution. The test is not valid unless the chloroform layer obtained in the blank determination is colourless.

**Residue on Ignition.** Not more than 0.1%, determined on 5g of the sub-divided sample in a suitable tared crucible. Ignite to constant weight in a muffle furnace at 800 ± 25°C. Allow the crucible to cool in a desiccator after each ignition.

**Biological Tests.** Perform the test for Biological Reactivity, In Vitro (2.2.23). Materials that meet the requirements of this test are not required to undergo testing as described in test for Biological Reactivity, In Vivo (2.2.24).

Plastic containers (whether based on PET or other plastics) for parenteral preparations shall be governed by all considerations covered in details in 6.1.1.2.

6.1.1.1. Sterile Plastic Containers for 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 for manufacture of the containers are approved/registered by the appropriate competent authorities in accordance with the relevant national legislation and international agreements.

When the composition of the materials of the different parts of the containers corresponds to the appropriate specifications, their quality is controlled by the methods indicated in the specifications, described under Plastic Containers for Parenteral Preparations (6.1.1.1).

Materials other than those described in the Pharmacopoeia may be used provided that their composition is authorised by the Licensing 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 and do not 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 should be such as to ensure the maintenance of sterility. They should be easily removable but should be tamper-proof.

The capacity of the containers 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.

**Description.** 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 100mL of sodium chloride injection. Close the container and heat it in an autoclave so that the contents are maintained at 110°C for 30 minutes.

If the container under examination contains an anticoagulant solution, first empty it, rinse the container with 250 mL of *water for injections* at 20±1°C and discard the rinsings.

**Solution S₂.** Introduce into the container a volume of water for injections 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 minutes. After cooling, add sufficient water for injections to fill the container to its nominal capacity.

If the container under examination contains an anticoagulant solution, first empty it and rinse it as indicated above.

**Resistance to centrifugation.** Introduce into the container a volume of *water*, acidified by the addition of 1mL of *dilute hydrochloric acid*, sufficient to fill it to its nominal capacity. Envelop the container with absorbent paper impregnated with a 1 in 5 dilution of *bromophenol blue* reagent or other suitable indicator and then dried. Centrifuge at 5000 rpm for 10 minutes. No leakage is perceptible on the indicator paper and no permanent distortion occurs.

**Resistance to stretch.** Introduce into the container a volume of *water*, acidified by the addition of 1mL of *dilute hydrochloric acid*, 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 seconds. Repeat the test with the force applied to each of the parts for filling and emptying. No break and no deterioration occurs.

**Leakage.** Place the container that has been submitted to the stretch test between two plates covered with absorbent paper impregnated with a 1 in 5 dilution of *bromophenol blue* reagent 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 minute. Maintain the pressure for 10 minutes. 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 *sodium chloride injection* 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 injection*. Close the container, weigh it and store it at 5 ± 1°C in an atmosphere with a relative humidity of 50 ± 5% for 21 days. At the end of this period the loss in weight is not more than 1%.

**Emptying under pressure.** Fill the container with a volume of *water* 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 minutes.

**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 33.5% w/v solution of *sucrose* 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 minutes 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 hours. Raise the temperature to 50°C and maintain for 12 hours. 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 described above.

**Transparency.** Fill the empty container with a volume equal to its nominal capacity of the standard suspension (2.4.1), diluted so as to have an absorbance at 640nm of 0.37 to 0.43 (dilution factor about 1 in 16) (2.4.7). The cloudiness of the suspension must be perceptible when viewed through the bag, as compared with a similar container filled with water.

**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 described, 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 90.0g of sodium chloride, 34.6g of sodium phosphate and 2.4g of sodium dihydrogen phosphate dihydrate in water and dilute to 1000mL with the same solvent. Prepare three buffer solutions as follows:

- **Buffer solution A₀.** To 30.0mL of stock buffer solution add 10.0mL of water.
- **Buffer solution B₀.** To 30.0mL of stock buffer solution add 20.0mL of water.
- **Buffer solution C₀.** To 15.0mL of stock buffer solution add 85.0mL of water.

Introduce 1.4mL of solution S₂ into each of three centrifuge tubes. To tube I add 0.1mL of buffer solution A₀, to tube II add 0.1mL of buffer solution B₀ and to tube III add 0.1mL of buffer solution C₀. To each tube add 0.02mL 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 hours previously or blood collected into either an anticoagulant citrate phosphate dextrose solution (CPD solution) or anticoagulant citrate phosphate dextrose adenine solution (CPDA solution) less than 24 hours previously.

Prepare further three solutions as follows:

- 3.0mL of buffer solution A₀ and 12.0mL of water (solution A₁),
- 4.0mL of buffer solution B₀ and 11.0mL of water (solution B₁),
- 4.75mL of buffer solution B₀ and 10.25mL of water (solution C₁),

To tubes I, II and III add, respectively, 1.5mL of solution A₁, 1.5mL of solution B₁ and 1.5mL of solution C₁. At the same time and in the same manner, prepare three other tubes, replacing solution S₂ by water. Centrifuge simultaneously the tubes to be examined and the control tubes at exactly 2500g in the same horizontal centrifuge for 5 minutes. After centrifuging, measure the absorbance of the liquids at about 540nm (2.4.7), using the stock buffer solution as blank. Calculate the haemolytic value as a percentage from the expression

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

where, \( A_{100} \) = absorbance of tube III,

\( A_{exp} \) = absorbance of tube I or II or of the corresponding control tubes.

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

**Sterility.** Introduce aseptically into the container 100mL of sodium chloride injection and shake the container to ensure that the internal surfaces have been entirely wetted. Filter the contents of the container through a membrane filter. Complete the test as described under Method of Test for aqueous solutions (2.2.11), paragraph 2, beginning at the words ‘After filtration, ………’.

**Pyrogens.** Solution S₁ complies with the test for pyrogens (2.2.8). Inject 10mL of the solution per kilogram of the rabbit’s weight.
Abnormal toxicity. Solution $S_1$ complies with the general test for abnormal toxicity (2.2.1). Inject 0.5mL of the solution into each mouse.

Container and Closures. Sterile plastic containers for human blood and blood components are packed in protective tamper-evident 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.

The protective envelope is sealed in such a manner that it cannot be opened and re-closed without leaving visible traces that the seal has been broken.

Labelling. The label states (1) the date after which the content is not intended to be used; (2) that once withdrawn from its protective envelope, the content must be used within 10 days.

A part of the label is reserved for the information required concerning the blood or blood components for which the container is intended to be used.

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.

6.1.1.1.2. Empty Sterile Containers of Plasticised Poly(vinyl chloride) for Blood and Blood Components

Empty sterile containers of plasticised poly(vinyl chloride) for blood and blood components should meet the requirements described under the introductory part of section 6.1.1.of chapter 6.1. They also comply with the tests described under sterile plastic containers for blood and blood components and with the following additional tests.

Acidity or alkalinity. Introduce into the container a volume of water for injections corresponding to the intended volume of anticoagulant solution. Close the container and heat in an autoclave so that the contents are maintained at 110°C for 30 minutes. Cool and add sufficient water for injections to fill the container to its nominal capacity (solution A). To a volume of solution A corresponding to 4% of the nominal capacity of the container add 0.1mL of phenolphthalein solution; the solution remains colourless. Add 0.4mL of 0.1M sodium hydroxide; the solution is pink. Add 0.8mL of 0.01M hydrochloric acid and 0.1mL of methyl red solution; the solution is orange-red or red.

Light absorption. Heat water for injections in a round bottom flask in an autoclave at 110°C for 30 minutes (solution B). Measure the light absorption of solution A in the range 230nm to 250nm and not more than 0.10 at any wavelength from 251nm to 360nm (2.4.7).

Ammonium. Dilute 5mL of solution A to 14mL with water in a test-tube, if necessary make alkaline with 2M sodium hydroxide and dilute further to 15mL with water. Add 0.3mL of alkaline potassium mercuri-iodide solution, stopper the tube, mix and allow to stand for 5 minutes. When viewed vertically, any yellow colour produced is not more intense than that obtained by treating a mixture of 10mL of ammonium standard solution (1ppm NH₄) and 5mL of water in the same manner (2pm).

Chlorides. 15mL of solution A complies with the limit test for chlorides (2.3.12). Prepare the standard using a mixture of 1.2mL of chloride standard solution (5ppm CI) and 13.8mL of water (0.4ppm).

Extractable di(2-ethylhexyl)phthalate

Extraction solvent. Ethanol diluted with water to have a relative density of 0.9389 to 0.9395 (2.4.29), measured with a pycnometer.

Stock solution. Dissolve 0.1g of di(2-ethylhexyl)phthalate in the extraction solvent and dilute to 100mL with the same solvent.

Standard solutions

(a) Dilute 20mL of stock solution to 100mL with extraction solvent.
(b) Dilute 10mL of stock solution to 100mL with extraction solvent.
(c) Dilute 5mL of stock solution to 100mL with extraction solvent.
(d) Dilute 2mL of stock solution to 100mL with extraction solvent.
(e) Dilute 1mL of stock solution to 100mL with extraction solvent.

Measure the absorbance of the standard solutions at the maximum at about 272nm, using the extraction solvent as blank and plot a curve of absorbance against the concentration of di(2-ethylhexyl)phthalate (2.4.7).

Extraction procedure. Using the donor tubing and the needle or adaptor, fill the empty container with a volume equal to half the nominal volume with the extraction solvent, previously heated to 37°C in a well-stoppered flask. Expel the air completely from the container and seal the donor tube. Immerse the filled container in a horizontal position in a water-bath maintained at 37±1°C for 60±1 minute without shaking. Remove the container from the water-bath, invert it gently ten times and transfer the contents to a glass flask. Immediately measure the absorbance at the maximum at about 272nm, using the extraction solvent as blank (2.4.7).
Determine the concentration of di(2-ethylhexyl)phthalate in milligrams per 100mL of the extract from the calibration curve. The concentration does not exceed

10mg per 100mL for containers of nominal volume greater than 300mL but not greater than 500mL;
13mg per 100mL for containers of nominal volume greater than 150mL but not greater than 300mL;
14mg per 100mL for containers of nominal volume up to 150mL.

**Oxidisable substances.** Immediately after preparation of solution A, transfer to a borosilicate-glass flask a quantity corresponding to 8% of the nominal capacity of the container. At the same time, prepare a blank using an equal volume of the freshly prepared solution B in another borosilicate-glass flask. To each solution add 20.0mL of 0.002M potassium permanganate and 1mL of 1M sulphuric acid. Allow to stand at room temperature, protected from light, for 15 minutes. To each solution add 0.1g of potassium iodide. Allow to stand protected from light for 5 minutes and titrate immediately with 0.01M sodium thiosulphate, using 0.25mL of starch solution as indicator. The difference between the two titrations is not more than 2.0mL.

**Residue on evaporation.** Evaporate to dryness 100mL of solution A in a borosilicate-glass beaker, previously heated to 105ºC. Evaporate to dryness in the same conditions 100mL of solution B. Dry to constant weight at 105ºC. The difference between the weights of the residues is not more than 3mg.

### 6.1.1.3. Sterile Containers of Plasticised Poly(vinyl chloride) for Blood containing an Anticoagulant Solution

Unless otherwise authorised as described in the introductory part of section 6.1.1 of chapter 6.1, the nature and composition of the material from which the containers are made complies with the requirements described under Empty sterile containers of plasticised poly(vinyl chloride) for blood and blood components (6.1.1.1.2).

Sterile plastic containers containing an anticoagulant solution are used for the collection, storage and administration of blood. Before filling they comply with the description and characteristics described under Empty sterile containers of plasticised poly(vinyl chloride) for blood and blood components (6.1.1.1.2).

After addition of the anticoagulant solution the containers comply with the tests described under Sterile plastic containers for blood and blood components (6.1.1.1.1) and with the following additional tests:

**Light absorption.** Measure the light absorption of the anticoagulant solution from the container in the range 250 nm to 350nm using an anticoagulant solution of the same composition that has not been in contact with a plastic material as blank. The absorbance at the maximum at about 280nm is not more than 0.5 (2.4.7).

**Extractable di(2-ethylhexyl)phthalate.** Carefully remove the anticoagulant solution by means of the flexible transfer tube. Using a funnel fitted to the tube, completely fill the container with water, leave in contact for 1 minute, squeezing the container gently and empty completely. Repeat the rinsing. The container then complies with the test described under Empty sterile containers of plasticised poly(vinyl chloride) for blood and blood components (6.1.1.1.2).

**Volume of anticoagulant solution.** The volume does not differ by ±10% from the stated volume when determined by emptying the container and collecting the anticoagulant solution in a graduated cylinder.

### 6.1.1.2. Plastic Containers for Non-parenteral Preparations

**Leakage test.** Fill ten containers with water, fit with the intended closures and keep them inverted at room temperature for 24 hours. There are no signs of leakage from any container.

**Collapsibility test.** This test is applicable to containers which are to be squeezed in order to remove the contents. A container, by collapsing inward during use, yields at least 90% of its nominal contents at the required rate of flow at ambient temperature.

The following tests are applicable to containers intended for filling oral liquids.

**Clarity of aqueous extract.** Select unlabelled, unmarked and non-laminated portions from suitable containers, taken at random, sufficient to yield a total area of sample required, taking into account the surface area of both sides. Cut these portions into strips, none of which has a total area of more than 20cm². Wash the strips free from extraneous matter by shaking them with at least two separate portions of distilled water for about 30 seconds in each case, then draining off the water thoroughly.

Select cut and washed portions of the sample with a total surface area of 1250cm², transfer to a flask, previously cleaned with chromic acid mixture and rinsed with several portions of distilled water and add 250mL of distilled water. Cover the flask with a beaker and autoclave at 121ºC for 30 minutes. Carry out a blank determination using 250mL of distilled water. Cool and examine the extract; it is colourless and free from turbidity.

**Non-volatile residue.** Evaporate 100mL of the extract obtained in the test for Clarity of aqueous extract to dryness and dry to constant weight at 105ºC. The residue weighs not more than 12.5mg.
6.1.1.2.1. Containers based on PET (Polyethylene Terephthalate)

Polyesters are polymers containing ester linkages generated due to the condensation of di-acids and di-ols. A prominent example in the class of polyesters is Polyethylene terephthalate (PET).

PET is a polymer which comprises at least 85% units of terephthalic acid or dimethyl terephthalate condensed with ethylene glycol. Co-monomers such as isophthalic acid, dimethyl isophthalate or diethylene glycol may also be used in the PET polymerisation.

PRODUCTION OF PET

The polymerisation of PET is catalysed with catalyst (usually certain metal oxides), at temperatures greater than 280°C and high vacuum. The manufacturing process of the PET pellets (resin) should ensure that the residual acetaldehyde content is not greater than 10ppm.

The resin is then given shape into bottles or any other shape through a conversion process involving injection moulding and blow moulding.

The resin and its conversion into PET containers may involve the use of colorants conforming to Indian Standards IS-9833 and/or additives conforming to IS-12252.

QUALITY ASSESSMENT OF PET CONTAINERS

The container is deemed as safe for packaging of pharmaceutical formulations when it fulfils all the requirements of this monograph.

A] IDENTIFICATION OF CONTAINER MATERIAL

Test 1 – By FTIR Spectrophotometry

Dissolve 50mg of the PET container specimen under examination in 2mL of solvent blend of phenol and tetrachloroethane (60:40 w/w) or 1,1,1,3,3,3-hexafluoropropan-2-ol or other appropriate solvent systems. Apply several drops of this solution on a glass plate. Keep this plate on a water-bath in a fume cupboard to produce a thin film of about 15mm by 15mm. Allow the solvent to evaporate completely. Remove the film using a stream of water and a scraper. Dry the film in an oven (typically at 100-105°C for about 1 hours). Examine the film by infrared absorption spectrophotometry (2.4.6). The spectrum should show maxima at about 1725 cm\(^{-1}\), 1410 cm\(^{-1}\), 1265 cm\(^{-1}\), 1120 cm\(^{-1}\), 1100 cm\(^{-1}\), 1020 cm\(^{-1}\), 875 cm\(^{-1}\), and 725 cm\(^{-1}\).

Test 2 – By UV Spectrophotometry

Reflux 100mg of the PET container under examination with 250mL of a 20% w/v solution of potassium hydroxide in a 50% v/v solution of ethanol for 30 minutes in a round bottom flask. Allow to cool and dilute to 100mL with water. Filter if necessary. Dilute 1.0mL of the filtrate to 100mL with water. Examine this solution in the range 210nm and 330nm (2.4.7), the absorption maximum should be at about 240nm.

B] CHEMICAL TESTS

B1] TESTS USING SPECIAL SOLUTIONS

Preparation of Special Solutions for Subsequent Tests

Select unlabelled, unmarked and non-laminated portions from suitable containers, taken at random, sufficient to yield a total area of sample required, cut these portions into strips, none of which has a total area of more than 1cm\(^2\).

Solution S1

Place 10g of the sample in a round bottom flask. Add 200mL of water and heat at 50°C for 5 hours. Allow to cool and then decant the solution. Use solution S1 within 4 hours of its preparation.

Solution S2

Place 10 g of the sample in a round bottom flask. Add 100mL of ethanol (95%) and heat at 50°C for 5 hours. Allow to cool and decant the solution. Use solution S2 within 4 hours of its preparation.

Solution S3

Place 20g of the sample in a round bottom flask. Add 50mL of 0.1 M hydrochloric acid and heat at 50°C for 5 hours. Allow to cool and decant the solution. Use solution S3 within 4 hours of its preparation.
Solution S4
Place 20 g of the sample into a round bottom flask. Add 50mL of 0.01 M sodium hydroxide and heat at 50°C for 5 hours. Allow to cool and decant. Use solution S4 within 4 hours of its preparation.

TESTS USING THE SPECIAL SOLUTIONS

B1.1 Appearance
Solution S1 has to be clear (2.4.1).
Solution S2 has to be clear and colourless (2.4.1).

B1.2 Acidity
To 50mL of solution S1 add 0.15mL of BRP indicator solution. The solution turns yellow. Not more than 0.5mL of 0.01 M sodium hydroxide is required to change the colour of the indicator to blue.

B1.3 Alkalinity
To 50mL of solution S1, add 0.2mL of methyl orange solution. The solution turns yellow. Not more than 0.5mL of 0.01M hydrochloric acid is required to reach the beginning of the colour change of the indicator to orange.

B1.4 Absorbance of solution S1 (2.4.7)
- In the UV-range (220nm to 340nm): Maximum absorbance should be 0.20
- In the visible range (400nm to 800nm): Maximum absorbance should be 0.05

B1.5 Absorbance of solution S2 (2.4.7)
In the visible range (400nm to 800nm): maximum absorbance should be 0.05

B1.6 Reducing substances
To 20mL of solution S1, add 2mL of 0.5 M sulphuric acid and 20mL of 0.002 M potassium permanganate. Boil for 3 minutes. Immediately cool to room temperature. Add 1.0g of potassium iodide, 0.25mL of starch solution as indicator and titrate with 0.01 M sodium thiosulphate. Perform a blank titration using 20mL of water.
The difference in volume used in the 2 titrations is not greater than 0.5mL.

B1.7 Extractable metals
NOTE- For quantitative determination of all the following metals Inductively Coupled Plasma Spectrometry (2.4.42) may be used. Alternatively, Atomic Absorption Spectrometry (2.4.2) can be used provided it has the appropriate sensitivity.

USE TEST SOLUTION S3 FOR THE FOLLOWING ESTIMATIONS

B1.7.1 Aluminium. Not more than 1ppm.
Reference solutions. Prepare the reference solutions using aluminium standard solution (200ppm Al), diluting with 0.1 M hydrochloric acid.
Wavelength 396.15nm, the spectral background being taken at 396.25nm.
Verify the absence of aluminium in the 0.1 M hydrochloric acid used.

B1.7.2 Barium. Not more than 1ppm.
Reference solutions. Prepare the reference solutions using barium standard solution (50ppm Ba), diluting with 0.1 M hydrochloric acid.
Wavelength 455.40nm, the spectral background being taken at 455.30nm.
Verify the absence of barium in the 0.1 M hydrochloric acid used.

B1.7.3 Cobalt. Not more than 1ppm.
Reference solutions. Prepare the reference solutions using cobalt standard solution (100ppm Co), diluting with 0.1 M hydrochloric acid.
Wavelength 228.62nm, the spectral background being taken at 228.50nm.
Verify the absence of cobalt in the 0.1 M hydrochloric acid used.

B1.7.4 Manganese. Not more than 1ppm.
Reference solutions. Prepare the reference solutions using manganese standard solution (100ppm Mn), diluting with 0.1 M hydrochloric acid.
Wavelength 257.61nm, the spectral background being taken at 257.50nm.
Verify the absence of manganese in the 0.1 M hydrochloric acid used.
B1.7.5 **Titanium.** Not more than 1ppm.

*Reference solutions.* Prepare the reference solutions using *titanium standard solution (100ppm Ti)*, diluting with *0.1 M hydrochloric acid.*

*Wavelength* 323.45nm or 334.94nm, the spectral background being taken at 323.35nm. Verify the absence of titanium in the *0.1 M hydrochloric acid* used.

B1.7.6 **Zinc.** Not more than 1ppm.

*Reference solutions.* Prepare the reference solutions using *zinc standard solution (100ppm Zn)*, diluting with *0.1 M hydrochloric acid.*

*Wavelength* 213.86nm, the spectral background being taken at 213.75nm. Verify the absence of zinc in the *0.1 M hydrochloric acid* used.

**USE TEST SOLUTION S4 FOR THE FOLLOWING ESTIMATIONS**

B1.7.7 **Antimony.** Not more than 1ppm.

*Reference solutions.* Prepare the reference solutions using *antimony standard solution (100ppm Sb)*, diluting with *0.01 M sodium hydroxide.*

*Wavelength* 231.15nm or 217.58nm, the spectral background being taken at 231.05nm.

B1.7.8 **Germanium.** Not more than 1ppm.

*Reference solutions.* Prepare the reference solutions using *germanium standard solution (100ppm Ge)*, diluting with *0.01 M sodium hydroxide.*

*Wavelength* 206.87nm or 265.12nm, the spectral background being taken at 206.75nm.

B2] **OTHER TESTS**

B2.1 **Substances soluble in dioxin**

Not more than 3.0%.

Place 2g of the material to be examined in a round bottom flask. Add 20mL of *dioxan* and heat under reflux for 2 hours. Evaporate 10mL of the solution to dryness on a water-bath and then dry the residue at 100-105°C.

The residue weighs a maximum of 30.0mg.

B2.2 **Sulphated ash (2.3.18)**

Not more than 0.5% determined on 1.0g.

B2.3 **Total Terephthaloyl moieties**

Not more than 1ppm

*Polyethylene terephthalate extracting media.* (1) *50% ethanol* (dilute 125mL of *ethanol (95%)*, with *Purified Water* to 238mL, and mix), (2) *n-heptane* and (3) *water*.

For each extracting media fill a sufficient number of test containers to 90% of its nominal capacity to obtain not less than 30mL.

Fill a corresponding number of glass bottles with each extracting medium for use as a blank. Fit the bottles with impervious seals, such as aluminium foil, or apply closures. Incubate the test packaging system and the glass bottles at 49°C for 10 days. Remove the test systems and glass bottles and store at room temperature. Do not transfer the *extracting medium* samples to alternative storage vessel.

Determine the absorbance of *50% ethanol* extract at the wavelength of maximum absorbance at about 244nm (2.4.7). For the blank use corresponding extracting medium blank.

Determine the absorbance of *n-heptane* extract at the wavelength of maximum absorbance at about 240nm (2.4.7). For the blank use corresponding extracting medium blank.

The absorbance of the *50% ethanol* and *n-heptane* extracts does not exceed 0.150, corresponding to not more than 1ppm of total terephthaloyl moieties.

B2.4 **Ethylene glycol**

Not more than 1ppm

*Periodic acid solution.* Dissolve 125 mg of periodic acid in 10mL of *water*.

*Dilute sulphuric acid.* To 50mL of *water*, slowly add and with constant stirring 50mL of *sulphuric acid*, allow to cool to room temperature.

*Sodium bisulphite solution.* Dissolve 100mg of *sodium bisulphite* in 10mL of *water*.

*Disodium chromotropate solution.* Dissolve 100mg of *disodium chromotropate* in 100mL of *sulphuric acid*. 
Reference solution. Dissolve quantity of ethylene glycol in the water, to obtain a solution containing 0.0001% w/v of ethylene glycol.

Test solution. Use the water extract from Total Terephthaloyl moieties

Procedure. Transfer 1mL of the reference solution, test solution and purified water extracting medium in three separate volumetric flasks. Add 0.1mL of periodic acid solution to each flask swirl to mix, and allow to stand for 60 minutes. Add 1mL of sodium bisulphite solution to each flask, and mix. Add 0.1mL of disodium chromotropate solution to each flask, and mix. (Note- All the solutions should be analysed within 1 hour after addition of disodium chromotropate solution) Slowly add 6mL of sulphuric acid to each flask, mix, and allow the solutions to cool to room temperature. Dilute each solution with dilute sulphuric acid to volume, and mix. Measure the absorbance of the resulting solutions at the maximum at about 575nm (2.4.7), using water extracting medium as the blank.

NOTE: Dilution of sulphuric acid produces substantial heat and can cause the solution to boil. Perform this addition carefully sulphur dioxide gas will be evolved. Use fume hood is recommended.

The absorbance of the Sample solution does not exceed that of the Standard solution, corresponding to not more than 1ppm of ethylene glycol.

C] BIOLOGICAL TESTS

Applicability of the test.

1. PET Containers to be used for the packaging of dosage forms other than oral and topical shall comply with the requirements stated in 6.2.3.

2. PET Containers to be used for the packaging of oral and topical dosage forms do not require the biological tests.

6.1.1.2.2. Containers based on other Plastics

6.1.1.3. Plastic Containers for Ophthamal Preparations

Plastic containers for ophthalmic preparations are made from plastic composed of a mixture of homologous compounds having a range of molecular weights. Such plastics frequently contain other substances such as residues from the polymerisation process, plasticisers, stabilisers, antioxidants, lubricants and pigments. For deciding the suitability of a plastic for use as a container for ophthalmic preparations, factors such as the composition of the plastic, processing and cleaning procedures, contacting media, adhesives, adsorption and permeability of preservatives, conditions of storage, etc. should be evaluated by appropriate additional specific tests.

Plastic containers for ophthalmic preparations comply with the following tests.

Leakage test; Collapsibility test; Clarity of aqueous extract; Non-volatile residue. Comply with the tests described under Plastic containers for Non-parenteral Preparations.

Eye irritation test. This test is designed to evaluate responses to the instillation of extracts of material under examination in the eye of a rabbit.

Extracting media – (a) Sodium Chloride Injection (b) Vegetable Oil.

Test animals. Select healthy, albino rabbits having no visible eye irritation and not previously used for an eye irritation test. The animal house should be designed and maintained so as to exclude sawdust, wood chips, or other extraneous materials that might produce eye irritation. Examine both eyes of the animals before testing and use only those animals without eye defects or eye irritations.

To test the suitability of the rabbit ocular system in use for a given set of samples, select one test animal and proceed as shown under procedure using 100µl of a blank prepared as directed under Systemic injection test in one eye and 100µl of sterile water for injection in the other eye. The rabbit ocular system is suitable if no significant differences are found between the two eyes.

Procedure. Use three albino rabbits for each extract to be examined. Restrain the animals firmly but gently until quiet. Gently pull the lower lid away from the eyeball to form a cup, and instil about 100µl of sterile water for injection. Hold the lid together for about 30 seconds. Instil in to the other eye 100µl of the sample extract prepared as directed under Systemic injection test. Examine the eyes 24, 48 and 72 hours after instillation. The requirements of the test are met if the sample extract shows no significant irritant response during the observation period over that with the blank extract and the rabbit ocular system is suitable. If irritation is observed in the control eyes treated with sterile water for injection or if the rabbit ocular system is shown not to be suitable, repeat the test using three additional rabbits. In the repeat test, all the rabbits meet the test requirement.

Biological Tests. Perform the test for Biological Reactivity, In Vitro (2.2.23). Materials that meet the requirements of this test are not required to undergo testing as described in test for Biological Reactivity, In Vivo (2.2.24).
6.1.2. Metal Containers

6.1.2.1. Collapsible Metal Tubes

For Ophthalmic Ointments- Metal collapsible tubes comply with the following test for metal particles.

Select a sample of 50 tubes from the lot to be tested and clean each tube by vibration and/or “blowing”. (A lot may be either the tube manufacturer’s day’s production or a consignment delivered to the tube user). Fill the tubes with a suitable molten eye ointment base, close the open end of each tube by a double fold and allow the filled tubes to cool overnight at a temperature of 15ºC to 20ºC.

Assemble a metal bacteriological filter with a 4.25-cm filter paper of suitable porosity supported on suitable perforated plate in place of the standard sintered carbon disc and heat it in a suitable manner to a temperature above the melting range of the base. Remove the caps from the cooled tubes and apply uniform pressure to the closed end of each tube in turn, in such a manner that the time taken to express as much of the base as possible through each nozzle is not less than 20 seconds. Collect the extruded base from the 50 tubes in the heated filter, applying suction to the stem of the filter in order to draw the molten base through the filter paper. When the entire melted base has been removed, wash the walls of the filter and the filter paper with three successive quantities, each of 30mL, of chloroform, allow the filter paper to dry and immediately mount it between glasses for examination.

Examine the filter paper under oblique lighting with the aid of magnifying glass with a graticule of 1mm squares, one of which is sub-divided into 0.2mm squares and note (a) the number of all metal particles 1mm in length and longer, (b) the number in the range 0.5mm to less than 1mm and (c) the number in the range 0.2mm to less than 0.5 mm.

Carry out two further examinations with the filter paper in two different positions so that the lighting comes from different directions and calculate the average number of metal particles counted in each of the three ranges specified. Give each metal particle detected on the filter paper a score as follows and add the scores together.

<table>
<thead>
<tr>
<th>Particles</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mm and above</td>
<td>50</td>
</tr>
<tr>
<td>0.5 mm but less than 1 mm</td>
<td>10</td>
</tr>
<tr>
<td>0.2 mm but less than 0.5 mm</td>
<td>2</td>
</tr>
<tr>
<td>less than 0.2 mm</td>
<td>Nil</td>
</tr>
</tbody>
</table>

The lot of tubes passes the test if the total score is less than 100 points; if the total score is more than 150 points, the lot fails the test. If the total score is between 100 and 150 (inclusive), the test is repeated on a further sample of 50 tubes and the lot passes the test if the sum of total scores in the two tests is less than 150 points.

For Non Ophthalmic Ointments-

6.1.2.2. Rigid Metal Containers

6.1.3. Glass Containers

Glass containers may be colourless or coloured.

Neutral glass is a borosilicate glass containing significant amounts of boric oxide, aluminium oxide, alkali and/or alkaline earth oxides. It has a high hydrolytic resistance and a high thermal shock resistance.

Soda-lime-silica glass is a silica glass containing alkali metal oxides, mainly sodium oxide and alkaline earth oxides, mainly calcium oxide. It has only a moderate hydrolytic resistance.

According to their hydrolytic resistance, glass containers are classified as:

- Type I glass containers which are of neutral glass, with a high hydrolytic resistance, suitable for most preparations whether or not for parenteral use,
- Type II glass containers which are usually of soda-lime-silica glass with high hydrolytic resistance resulting from suitable treatment of the surface. They are suitable for most acidic and neutral, aqueous preparations whether or not for parenteral use,
- Type III glass containers which are usually of soda-lime-silica glass with only moderate hydrolytic resistance. They are generally suitable for non-aqueous preparations for parenteral use, for powders for parenteral use (except for freeze-dried preparations) and for preparations not for parenteral use.

Glass containers intended for parenteral preparations may be ampoules, vials or bottles. The glass used in the manufacture of such containers complies with one of the requirements for hydrolytic resistance given below.

Containers of Type II or Type III glass should be used once only. Containers for human blood and blood components must not be re-used. Glass containers with a hydrolytic resistance higher than that recommended for a particular type of preparation may generally also be used.
Containers for parenteral preparations are made from uncoloured glass except that coloured glass may be used for substances known to be light-sensitive; in such cases, the containers should be sufficiently transparent to permit visual inspection of the contents.

**Hydrolytic resistance**

The tests to be done for defining the type of glass are given in Table 2.

<table>
<thead>
<tr>
<th>Type of container</th>
<th>Test to be done</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I and Type II glass containers to distinguish from Type III glass containers</td>
<td>Test 1 (surface test)</td>
</tr>
<tr>
<td>Type I and Type II glass containers where it is necessary to determine whether the high hydrolytic resistance is due to the chemical composition or the surface treatment</td>
<td>Tests 1 and 2</td>
</tr>
</tbody>
</table>

**Test 1.** Carry out the determination on the unused containers. The number of containers to be examined and the volumes of test solution to be used are given in Table 3.

<table>
<thead>
<tr>
<th>Nominal capacity of container (mL)</th>
<th>Number of containers to be used</th>
<th>Volume of test solution to be used for titration (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to 3</td>
<td>At least 20</td>
<td>25.0</td>
</tr>
<tr>
<td>5 or less</td>
<td>At least 10</td>
<td>50.0</td>
</tr>
<tr>
<td>6 to 30</td>
<td>At least 5</td>
<td>50.0</td>
</tr>
<tr>
<td>More than 30</td>
<td>At least 3</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Remove any debris or dust from the containers. Rinse each container at least twice with water at room temperature. Just before the test rinse each container with freshly prepared distilled water and allow to drain. Complete the cleaning procedure from the first rinsing in not less than 20 minutes and not more than 25 minutes. Fill the containers to the brim with freshly prepared distilled water, empty them and determine the average overflow volume.

Heat closed ampoules on a water-bath or in an air-oven at about 50°C. Fill the ampoules with freshly prepared distilled water to the maximum volume compatible with sealing them by fusion of the glass and seal them. Fill bottles or vials to 90% of their calculated overflow volume and cover them with borosilicate glass dishes or aluminium foil previously rinsed with freshly prepared distilled water. Place the containers in an autoclave containing water so that they remain clear of the water. Close the autoclave, displace the air by passage of steam for 10 minutes, raise the temperature from 100°C to 121°C over 20 minutes, maintain a temperature of 121°C for 60 minutes and reduce the temperature from 121°C to 100°C over 40 minutes, venting to prevent vacuum.

Remove the containers from the autoclave and cool them in a bath of running tap water. Carry out the following titration within 1 hour of removing the containers from the autoclave. Combine the liquids from the containers under examination, measure the volume of test solution specified in Table 2 into a conical flask and add 0.15mL of methyl red solution for each 50mL of liquid. Titrate with 0.01M hydrochloric acid taking as the end-point the colour obtained by repeating the operation using the same volume of freshly prepared distilled water. The difference between the preparations represents the volume of 0.01M hydrochloric acid required by the test solution. Calculate the volume of 0.01M hydrochloric acid required for each 100mL of test solution, if necessary. The result is not greater than the value stated in Table 4.

**Test 2.** Examine the number of containers indicated in Table 2. Rinse the containers twice with water and then fill completely with a 4% v/v solution of hydrofluoric acid and allow to stand at room temperature for 10 minutes. Empty the containers and rinse carefully five times with water. Carry out the procedure described under Hydrolytic resistance. Compare the results with the limiting values given in Table 3. For Type I glass the values obtained with the hydrofluoric acid-treated containers are closely similar to those stated in the Table for Type I or Type II glass. For Type II glass the values obtained with the hydrofluoric acid-treated containers greatly exceed those given in the Table for Type I or Type II glass and are similar to those given for Type III glass.
<table>
<thead>
<tr>
<th>Capacity of container</th>
<th>Volume of 0.01M hydrochloric acid per 100mL of test solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>[corresponding to 90% average overflow volume (mL)]</td>
<td>Type I or II glass (mL)</td>
</tr>
<tr>
<td>Not more than 1</td>
<td>2.0</td>
</tr>
<tr>
<td>More than 1 but not more than 2</td>
<td>1.8</td>
</tr>
<tr>
<td>More than 2 but not more than 5</td>
<td>1.3</td>
</tr>
<tr>
<td>More than 5 but not more than 10</td>
<td>1.0</td>
</tr>
<tr>
<td>More than 10 but not more than 20</td>
<td>0.80</td>
</tr>
<tr>
<td>More than 20 but not more than 50</td>
<td>0.60</td>
</tr>
<tr>
<td>More than 50 but not more than 100</td>
<td>0.50</td>
</tr>
<tr>
<td>More than 100 but not more than 200</td>
<td>0.40</td>
</tr>
<tr>
<td>More than 200 but not more than 500</td>
<td>0.30</td>
</tr>
<tr>
<td>More than 500</td>
<td>0.20</td>
</tr>
</tbody>
</table>

**Arsenic.** Glass containers for aqueous parenteral preparations should comply with the following test. Carry out the test on ampoules the inner and outer surfaces of which are washed five times with freshly distilled water.

Prepare a test solution as described in the test for Hydrolytic resistance for an adequate number of containers to produce 50mL. Pipette 10mL of the test solution from the combined contents of all the containers into a flask, add 10mL of nitric acid and evaporate to dryness on a water-bath. Dry the residue in an oven at 130°C for 30 minutes. Cool, add to the residue 10.0mL of hydrazine-molybdate reagent, swirl to dissolve and heat under reflux on a water-bath for 20 minutes. Cool to room temperature. Determine the absorbance of the resulting solution at the maximum at about 840nm (2.4.7), using 10.0mL of hydrazine-molybdate reagent as the blank. The absorbance of the test solution does not exceed the absorbance obtained by repeating the determination using 0.1mL of arsenic standard solution (10ppm As) in place of the test solution (0.1ppm).

### 6.2. Closures for Containers of Parenteral Products

A closure for a container for an aqueous parenteral preparation or for a sterile powder is a packaging component which is in direct contact with the drug. A rubber closure is made of materials obtained by vulcanisation (cross-linking) of elastomers with appropriate additives. The elastomers are produced from natural or synthetic substances by polymerisation, polyaddition or polycondensation. The nature of the principal components and of the various additives such as vulcanisers, accelerators, stabilising agents, pigments, etc. depends on the properties required for the finished closure. The requirements of this chapter do not apply to closures made from silicone elastomer, to laminated closures or to lacquered closures.

Rubber closures are used in a number of formulations and consequently different closures possess different properties.

Closures made from plastics will be governed by all stipulations covered in 6.1.1 and its subsections.

The closures chosen for use with a particular preparation should be such that the components of the preparation in contact with the closure are not adsorbed onto the surface of the closure to an extent sufficient to affect the product adversely. The closure should not yield to the product substances in quantities sufficient to affect its stability or to present a risk of toxicity. The closures should be compatible with the preparation for which they are used throughout the shelf-life of the product.

It is impracticable to devise a set of standards which, if complied with, will ensure the compatibility of any closure with the preparation for which it is to be used. A compatibility test has, therefore, to be carried out before a rubber mix is approved. The user of the closures must obtain an assurance from the supplier that the composition of the closure does not vary from supply to supply and that it is identical to that of the closure used during compatibility testing. When the user is informed of changes in the composition, compatibility testing must be repeated, totally or partly depending on the nature of the changes.

The following test procedures apply to rubber closures which comprise wads (flat rubber discs), plugs (with or without skirt or flange) and caps (rubber covers held in position on the outsides of the containers by the tension of the rubber) so as to form with their appropriate seals an effective barrier against micro-organisms after sterilisation.
Identification of the type of rubber used for closures is not covered in the following tests. The tests given distinguish elastomer and non-elastomer closures but do not differentiate the various types of rubber.

**Description.** Rubber closures are elastic and either translucent or opaque; the colour depends on the additives used. They are homogeneous and practically free from flash and adventitious materials such as fibres, foreign particles and adhering rubber pieces.

**Identification**

A. Heat 1g to 2g in a heat-resistant test-tube over an open flame to dry the sample and continue heating until the vapours formed are condensed near the top edge of the test-tube. Deposit a few drops of the condensate on a potassium bromide disc and examine by infrared absorption spectrophotometry (2.4.6), comparing with the spectrum obtained with the type (standard) sample.

B. The total ash (2.3.19) is within ±10% of the value obtained with the type sample.

**Preparation of samples.** Wash the closures by agitation in a 0.2% w/v solution of an anionic surface-active agent for 5 minutes at room temperature. Rinse five times with water, place a number of the washed closures corresponding to a surface area of about 100cm², in a suitable container of borosilicate glass or inert material, add 200mL of water per 100cm², surface area of the closures and weigh. Cover the mouth of the container with aluminium foil or a borosilicate glass beaker and heat in an autoclave so that a temperature of 119°C to 123°C is reached within 20 to 30 minutes and maintain at that temperature for 30 minutes. Cool to room temperature over about 30 minutes and make up to the original weight with water for injection. Shake and immediately separate the solution from the closures by decantation (Solution A).

Prepare a blank in the same manner using 200mL of water for injection.

Dry the treated closures at 64°C to 66°C at a pressure not exceeding 0.7 kPa for 24 hours.

**Appearance of solution.** Solution A is not more opalescent than opalescence standard OS3 (2.4.1), and not more intensely coloured than reference solution BYS6 (2.4.1).

**Acidity or alkalinity.** To 20mL of solution A add 0.1mL of bromothymol blue solution. Not more than 0.3mL of 0.01M sodium hydroxide or 0.8mL of 0.01M hydrochloric acid is required to change the colour of the solution to blue or yellow respectively.

**Light absorption.** Carry out the test within 4 hours of preparing solution A. Filter solution A through a membrane filter with a nominal pore size of 0.5μm and reject the first few mL of the filtrate. Measure the light absorption of the filtrate in the range 220 to 360nm (2.4.7), using as the blank a solution prepared in the same manner as solution A but using 200mL of water without the closures. The absorbance is not more than 2.0; if necessary, dilute the filtrate before measurement and correct the results for the dilution.

**Reducing substances.** Carry out the test within 4 hours of preparing solution A. To 20mL of solution A, add 1mL of 1M sulphuric acid and 20mL of 0.002 M potassium permanganate and boil for 3 minutes. Cool, add 1g of potassium iodide and titrate immediately with 0.01 M sodium thiosulphate using 0.25mL of starch solution, added towards the end of the titration, as indicator. Repeat the operation using 20 mL of the blank prepared in the test for Light absorption. The difference between the titration volumes is not more than 7.0mL.

**Heavy Metals (2.3.13).** 20mL of solution A complies with the limit test for heavy metals, Method A.

**Residue on evaporation.** Evaporate 50mL of solution A to dryness on a water-bath and dry at 105°C. The residue weighs not more than 4.0mg.

**Volatile sulphides.** Place closures, cut if necessary, with a total surface area of 20±2cm² in a 100-mL conical flask and add 50mL of a 2% w/v solution of citric acid. Place a piece of lead acetate paper over the mouth of the flask and maintain the paper in position by placing over it an inverted weighing bottle. Heat in an autoclave at 121±2°C for 30 minutes. Any black stain on the paper is not more intense than that of a standard prepared at the same time in the same manner using 0.154mg of sodium sulphide and 50mL of a 2% w/v solution of citric acid.

**Sterilisation test.** The closures ‘prepared’ in the aforementioned manner shall not soften or become tacky and there shall be no visual change in the closure.

**Fragmentation test.** This test is applicable to closures intended to be pierced by a hypodermic needle. For closures that are intended to be used for aqueous preparations, place a volume of water corresponding to the nominal volume minus 4mL in each of 12 clean vials, close the vials with the ‘prepared’ closures, secure with a cap and allow to stand for 16 hours. For closures that are intended to be used for dry preparations, close 12 clean vials with the ‘prepared’ closures. Using a lubricated, long-bevel (bevel angle of 10°C to 14°C) hypodermic needle with an external diameter of 0.8mm (21 SWG) fitted to a clean syringe, inject 1mL of water into the vial and remove 1 mL of air; carry out this operation 4 times for each closure, piercing each time at a different site. Use a new needle for each closure and check that the needle is not blunted during the test. Pass the liquid in the vials through a filter with a nominal pore size of 0.5μm. Count the number of fragments visible to the naked eye. The total number of
fragments is not more than 10 except in the case of butyl rubber closures where the total number of fragments is not more than 15.

**Self-sealability.** This test is applicable to closures intended to be used with multidose containers. Fill 10 suitable vials with water to the nominal volume, close the vials with the ‘prepared’ closures and secure with a cap. For each closure, use a new hypodermic needle with an external diameter of 0.8mm (21 SWG) and pierce the closure 10 times, piercing each time at a different site. Immerse the vials upright in a 0.1% w/v solution of methylene blue and reduce the external pressure by 27kPa for 10 minutes. Restore the atmospheric pressure and leave the vials immersed for 30 minutes. Rinse the outside of the vials. None of the vials contains any trace of coloured solution.

**Biological Tests.** Perform the test for Biological Reactivity, *In Vitro* (2.2.23). Materials that meet the requirements of this test are not required to undergo testing as described in test for Biological Reactivity, *In Vivo* (2.2.24).

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**To be inserted under General reagents.**

- **BRP Indicator Solution** Dissolve 0.1g of *bromothymol blue*, 20mg of *methyl red* and 0.2g of *phenolphthalein* in sufficient *ethanol* (95%) to produce 100mL. Filter.

- **Aluminium Standard Solution (200ppm Al)** Dissolve a quantity of *aluminium potassium sulphate* equivalent to 0.352g of AlK(SO₄)₂.12H₂O. Add 10.0mL of *dilute sulphuric acid* and dilute to 100mL with *water*.

- **Antimony standard solution (100ppm Sb)** Dissolve antimony potassium tartrate equivalent to 0.274g of C₄H₄KO₇Sb.½H₂O in 500mL of 1M *hydrochloric acid* and dilute the clear solution to 1000mL with *water*.

- **Cobalt standard solution (100ppm Co)** Dissolve cobalt nitrate equivalent to 0.494 g of Co(NO₃)₂.6H₂O in 500mL of 1M *nitric acid* and dilute the clear solution to 1000mL with *water*.

- **Germanium Standard Solution (100ppm Ge)** Dissolve ammonium hexafluorogermanate (IV) equivalent to 0.307 g of (NH₄)₂GeF₆ in a 0.01% v/v solution of *hydrofluoric acid*. Dilute the clear solution to 1000mL with *water*.

- **Ammonium Hexafluorogermanate (IV)** (NH₄)₂GeF₆ = 222.7. General reagent grade of commerce.

- **Hydrofluoric Acid.** HF = 20.01 (7664.39-3)
  - Content, minimum 40% w/w.
  - Clear, colourless liquid.
  - **Loss on ignition:** Not more than 0.05% w/w; evaporate the hydrofluoric acid in a platinum crucible and gently ignite the residue to constant mass.

- **Manganese Standard Solution (100ppm Mn)** Dissolve manganese sulphate equivalent to 0.308g of MnSO₄.H₂O in 500mL of 1M *nitric acid* and dilute the clear solution to 1000mL with *water*.

- **Titanium Standard Solution (100ppm Ti)** Dissolve 100mg of *titanium* in 100mL of *hydrochloric acid* diluted to 150mL with *water*, heating if necessary. Allow to cool and dilute to 1000mL with *water*.

- **Method for ICP-OES to be added.**