BEFORE THE HON'BLE GREEN TRIBUNAL AT NEW DELHI

ORIGINAL APPLICATION NO. 15 OF 2014

IN THE MATTER OF :

HIM JAGRITI UTTARANCHAL

WELFARE SOCIETY ...PETITIONER

VERSUS

UNION OF INDIA

...RESPONDENT

S.NO.	**Particulars**	**Page Nos.**
1.	Additional affidavit on behalf of respondents no. 03	**1-6**
2.	**Annexure A-1** A copy of Volume-1, page no.-1019-1060 of 8th Edition of Indian Pharmacopoeia (IP), 2018.	**7-47**
3.	**Annexure A-2** A copy of the Letter dated 27.01.2020	**48-50**
4.	PROOF OF SERVICE	51

KIRTIMAN SINGH
Advocate for the Petitioner
A-9, Lower Ground Floor
South Extension Part-I
New Delhi – 110045
Phone – 011-49071872
Mobile- 9811700872

Place-New Delhi
Date- 12.11.2020

BEFORE THE HON'BLE NATIONAL GREEN TRIBUNAL AT NEW DELHI

ORIGINAL APPLICATION NO. 15 OF 2014

IN THE MATTER OF :

HIM JAGRITI UTTARANCHAL WELFARE SOCIETY

.....PETITIONER

VERSUS

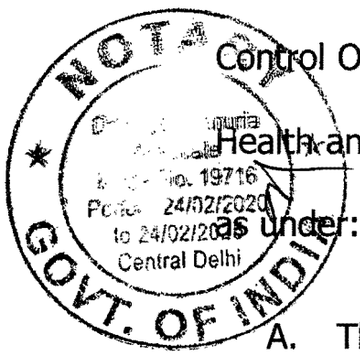
UNION OF INDIA & ANR

....RESPONDENT

ADDITIONAL AFFIDAVIT ON BEHALF OF RESPONDENTS No. 03

MOST RESPECTFULLY SHOWETH:-

I, Dr. P.B.N. Prasad, S/o Sh. P. Somaiah Naidu, aged about 57 years, working as Joint Drugs Controller (India), Central Drugs Standard Control Organisation, Directorate General of Health Services, Ministry of Health and Family Welfare, Govt. of India, do solemnly state and affirm as under:-



A. That I am the above named Deponent and am authorized and well conversant with the facts and circumstances of the present case on the basis of the records of the case and thus competent to swear the present affidavit.

B. The present reply affidavit is being filed in response to this Hon'ble Tribunal order dated 14.10.2019 & 10.09.2020. Unless

any averment / allegation / submission is not specifically admitted, the same may be treated as denied.

PRELIMINARY SUBMISSIONS:

1. The Drugs and Cosmetics Act, 1940 (hereinafter referred to as "Act"), is a central legislation, which regulates the import, manufacture, distribution and sale of drugs and cosmetics in the country. The main objective of the Act is to ensure that the drugs available to the people are safe and efficacious and conform to prescribed quality standards and the cosmetics marketed are safe for use.

2. A representation was received from the Him Jagriti, to impose a complete ban on usage of PET bottles (both coloured and uncolored) as primary packaging material in pharmaceutical liquid orals, suspensions and dry syrups was considered by Drugs Technical Advisory Board (DTAB) an statutory body under the Drugs and Cosmetics Act, 1940. Subsequently, Ministry of Health and Family Welfare published draft rules vide Gazette Notification No. G.S.R 701 (E) dated 29.09.2014 for prohibition of use of Polyethylene Terephthalate or plastic containers in liquid oral formulations for primary packaging of drug formulations for pediatric use, geriatric use and for use in case of pregnant women and women of reproductive age group.

3. That in view of the large number of objections and suggestions from various stakeholders on said draft rules the Ministry of

Health and Family Welfare constituted a high level committee under the chairmanship of Prof. M.K Bhan, the former Secretary, DBT, to review the safety of Polyethylene terephthalate (PET) and its containers for the packaging of pharmaceuticals.

4. It is respectfully submitted that this Hon'ble Tribunal in its order dated 14.10.2019, considered the report dated 30.08.2019 of the expert committee comprising FSSAI, BIS, CPCP and DGHS to consider whether any further regulatory provisions are required on the subject of restrictions on the packaging by use of plastic material and if so to what extent. Further the Hon'ble court in view of the report, directed to take further follow up action based on the said report and furnish an action taken report before the Tribunal.

5. It is respectfully submitted that for compliance of this Hon'ble Tribunal order dated 14.10.2019, FSSAI had requested the concerned agencies / departments including CDSCO vide Letter no. 1-95/stds/Misc/SP (L&C/A)/FSSAI-2015(pt-4) dated 05.11.2019 to initiate necessary action and accordingly to submit an Action taken report to FSSAI so that same could be compiled and submitted to the Hon'ble NGT by them.

6. It is respectfully submitted that on the basis of the recommendations of the M. K. Bhan committee, Indian Pharmacopoeia Commission, MoH&FW, Ghaziabad has examined the issue through an expert Committee under the Chairmanship of Prof. Y. K. Gupta, former Head of Dept. of Pharmacology, AIIMS, New Delhi, and revised the Chapter on "Primary Packages for

Pharmaceutical Articles"and same has been published in Volume-I, Page No.-1019 of 8th Edition of Indian Pharmacopoeia (IP), 2018. It includes standards of PET (Polyethylene terephthalate) as well as standards of other polymers/plastic containers and primary packaging of pharmaceuticals. Labels of on the containers are also revised to meet the requirements of Drug and Cosmetics Act, 1940 and Rules made there under.

A copy of Volume-I, Page No.-1019 to 1060 of 8th Edition of Indian Pharmacopoeia (IP), 2018 is annexed and marked as **Annexure-A1.**

7. It is respectfully submitted that accordingly the "Chapter 6. Primary Packages for Pharmaceutical Articles" of the IP has been harmonized at par with global Pharmacopoeias for ensuring safe use of plastics for packaging of pharmaceuticals.

8. Accordingly, CDSCO had submitted the Action taken report in respect of use Plastics for packaging of Pharmaceuticals to the FSSAI vide letter No. 29/Misc./38/2019-DC dated 27.01.2020, comprising the reply received from Indian Pharmacopoeia Commission, MoH&FW, Ghaziabad, as to "whether any further regulatory provisions are required on the use of plastics for packaging of pharmaceuticals, after the steps already taken, and if so, to what extent (copy attached).

A copy of Letter dated 27.01.2020 is annexed and marked as **Annexure-A2.**

9. It is respectfully submitted that manufacture, marketing & sale of Drugs are regulated under the provisions of Drugs and Cosmetics Act, 1940 and Rules made there under. Good manufacturing Practices and requirements of premises, plant and equipment for manufacture of Pharmaceutical products are specified in Schedule M to the Drugs and Cosmetics Rules, 1945.

10. As per the Schedule M to the said rules, all containers and closures intended for use shall comply with the Pharmacopeia and other specified requirements. Suitable sample sizes, specifications, test methods, cleaning procedures and sterilization procedures, shall be used to assure that containers, closures and other component parts of drug packages are suitable and are not reactive, additive, adsorptive or leachable or presents the risk of toxicity to an extent that significantly affects the quality or purity of the drug. No second hand or used containers and closures shall be used. Pharmaceutical manufacturers are required to follow the Standards laid down in Indian Pharmacopoeia.

In view of the aforesaid facts and circumstances, it is most respectfully submitted that the present petition may be disposed of and this Hon'ble Court may be further pleased to pass such other and further orders as it may deem fit and necessary.

DEPONENT

Dr. P. B. N. PRASAD
Joint Drugs Controller (India)
Central Drugs Standard Control Organisation
Dte. General of Health Services
Ministry of Health and Family Welfare
FDA Bhawan, Kotla Road, I.T.O., New Delhi-110002

VERIFICATION:

Verified at New Delhi on __ day of November 2020 that the contents of the above affidavit are true and correct on the basis of official records and nothing material has been concealed therefrom.

12 NOV 2020

I identified the deponent who has signed in my presence

DEPONENT

Dr. P. B. N. PRASAD
Joint Drugs Controller (India)
Central Drugs Standard Control Organisation
Dte. General of Health Services
Ministry of Health and Family Welfare
FDA Bhawan, Kotla Road, I.T.O., New Delhi-110002

NOTARY
GOVT. OF INDIA
Behuria
Advocate
Regn. No. 19716
Period 24/02/2020
to 24/02/2025
Central Delhi

CERTIFIED THAT THE DEPONENT
Shri / Smt. / Km : Dr. P.B.N. Prasad
S/o, W/o D/o : P. Someiah Naidu
I dentified by Shri / Smt. K. Hemanthura
Has solemnly affirmed before me at
Delhi on ...
That the contents of the affidavit which have been read & explained to him are true & correct to his knowledge

NOTARY

12 NOV 2020

Annexure - A 17

6. PRIMARY PACKAGES FOR PHARMACEUTICAL ARTICLES

6.1. Introduction

Pharmaceutical articles are delivered to the intended consumers in a variety of packages.

A package for pharmaceutical articles is a form that is intended to contain, protect or preserve the contents throughout the shelf life; aid in the safe, appropriate transportation and distribution; and to inform the user about the pharmaceutical article. A package comprises a container that usually has a closure (e.g. cap, lid, dispensing system) and a label (e.g. a separate label or printed matter). The closure may or may not have a liner.

A package is also conventionally referred to as a container-closure system.

*NOTE 1 — **Scope***

This section covers the primary package i.e. the materials that come in direct contact with pharmaceutical contents. Secondary and tertiary packageare not addressed in this pharmacopoeia.

This chapter deals with the specific requirements, guidance and information on containers used for packaging of pharmaceutical articles. The materials that are used in the manufacture of containers, particularly plastic containers, the raw materials and the additives used and the formulations employed should be agreed with the users of the containers.

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

A container-closure system for Pharmaceutical article 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-closure system for Pharmaceutical article 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-closure system for Pharmaceutical 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 label indicates the measures to be taken to protect the article from contamination and deterioration during its entire shelf-life. TechnicalSpecifications for the package to be used for any article have not been given but in certain cases, the type of package that is recommended is stated in terms that have the following meanings.

6.1.1. Terminology

a. ***Package***. A package comprises a container that usually has a closure (e.g. cap, lid, dispensing system) and a label (e.g. a separate label or printed matter). The closure may or may not have a liner.

   A package is also conventionally referred to as a container-closure system.

b. ***Well-closed Package***. A container-closure system for a Pharmaceutical article that protects the contents from extraneous solids and liquids and loss of the article in process of handling, shipment, storage and distribution.

c. ***Airtight or Tightly-closed Package***. A container-closure system for a Pharmaceutical article that protects the contents from contamination by extraneous solids, liquids, or vapours, loss or deterioration of the article from effervescence, deliquescence or evaporation during handling, shipment, storage and distribution. A tightly-closed container-closure system for a Pharmaceutical article must be capable of being tightly re-closed after use.

d. ***Hermetically Sealed Package***. A container-closure system for a Pharmaceutical article 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. A hermetically sealed container-closure system must beused for a single dose.

e. ***Light-resistant Package***. A container-closure system for a Pharmaceutical article 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 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.

f. ***Single-dose Package***. A container-closure system for Pharmaceutical articlethat holds a quantity of the preparation intended for total or partial use as a single administration.

g. ***Multi-dose Package***. A container-closure system for a Pharmaceutical article that holds a quantity of the preparation suitable for two or more doses.

h. ***Sealed Package***. A container-closure system for Pharmaceutical article closed by fusion of the material of the container.

i. ***Tamper-evident Package***. A container-closure system for a Pharmaceutical article fitted with a device or mechanism that reveals irreversibly whether the container has been opened.

The user of the container-closure system must obtain an assurance from the supplier that its composition does not vary from batch to batch and that it is identical to that used during compatibility testing.

When the user is informed of changes in the composition, compatibility testing and biological testing must be repeated, totally or partly depending on the nature of the changes.

A container-closure system for a Pharmaceutical article is available in different forms. Details of the commonly used components are given below:

6.2. CONTAINERS

Containers for pharmaceutical articles are made of a variety of materials such as different types of plastics, glass, metal and their combination. This section covers the guideline for each type of these container materials.

6.2.1. 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 (ethylene-vinyl acetate) (IS 13601). However, if the manufacturer of Pharmaceutical articles intends to use plastics made from polymers other than listed above, it should be justified and authorised by appropriate competent authority.

The plastic identification codes as mentioned in IS 14534 may be visibly marked on the plastic containers and/ or the label, wherever possible.

The plastic containers should be manufactured from materials that do not include in their composition any substances that can be extracted by the pharmaceutical contents in such quantities that alter the efficacy orstability of the product or present a toxic hazard. Recycling of excess material (shavings, dust, etc. from the container manufacturing plant) of well-defined nature and proportions may be permitted after appropriate validation. However, the use of post-manufactured material is strictly prohibited. Re-use of earlier-filled bottles is strictly prohibited.

For general information, a summary of the manufacture and usage of plastic containers and closures is provided in the Table 1.

Table 1 - Overview of the life cycle (stages) of Plastic Materials for Pharmacopoeial Articles

Stakeholder	Activity Involved	Governing Regulations in force	Examples
Plastic Resin Manufacturers	**Monomers** (Raw material) ↓ conversion into ↓ **Polymer** (Plastic Resin)	BIS Standards on composition of various packaging polymers (plastic resins)	Polyethylene terephthalate (PET) = IS 12252 Polyethylene (PE) = IS 10146 Polyvinyl chloride (PVC) = IS 10151 Polypropylene (PP) = IS 10910 Polyamides [nylon 6] = IS 12247 Polycarbonate = IS 14971 Poly (ethylene-vinyl acetate) = IS 13601
Manufacturers of Packaging components (Convertors)	Addition of Colourant/ Additives to Resin if neededand converting the mixture into shaped articles(Plastics Articles)	BIS Standard for Resin Identification Codes IS - 14534	Bottles, Containers, Tubes, Caps, Closures and other forms of Packages **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 = PPCode No.6 = PS (Polystyrene) Code No.7 = Other plastics
Manufacturer of Pharmacopoeial Articles (Users)	Filling of Pharmaceutical Formulations (Packaged Products)	The Drugs and Cosmetics Act, 1940 The Drugs and Cosmetics Rules, 1945	Substances, Preparations, Articles
Consumer	Consumption/Usage	---	Patients, Health care chain (Doctors, Hospitals)
All stakeholders	Disposal	Plastic Waste Management Rules, 2016	Various responsibilities on Manufacturers, Local Bodies, Citizens, etc.

The selection of a suitable plastic container should be based on a knowledge - obtained from the supplier - of the composition of the plastic (e.g. raw materials, colourants and additives) so that potential hazards can be assessed.

The plastic container chosen for any particular pharmaceutical product should be such that the ingredients of the product in contact with the container do not significantly interact or migrate into or through the plastic, to a level that affects the quality of the product.

Test on Container Material

Type samples (specimen) 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 (specimen) 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 post-consumer recycled material. It must be emphasized that changes in the composition of the plastic or 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 (specimen) and test schedules should be designed to check deviations from the characteristic of the type sample (specimen).

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.

*NOTE 2 — **Applicability of Biological Tests for Plastic Packages***

a) Packages used for non-parenteral dosage forms do not require any biological testing.

b) Packages used forparenteral dosage forms require *in vitro* testing (2.2.23).

c) Packages that meet the requirements of the *in vitro* tests are not required to undergo any further *in vivo* testing (2.2.24).

d) Packages that do not meet the requirements of the *in vitro* tests where applicable are required to undergo further *in vivo* testing.

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

NOTE 3 —**Responsibility**

It shall be the responsibility of the user/manufacturer to ensure the compatibility of the pharmaceutical articles with the package and stability of the product in a package.

Towards this:

a) The user/manufacturer shall have in place a system of quality assurance with the supplier / convertor to ensure compliance of the components of the package with the requirement stated in this chapter at all times.

b) The initial protocol for approving the vendor and its packaging materials shall involve the entire test regimen as detailed in subsequent relevant sections of this chapter. Subsequently for every lot of the packaging materials only the following tests shall be carried out by the user (pharmaceutical manufacturers) :

   i. FTIR
   ii. Visual Inspection
   iii. Leakage
   iv. All tests related to appearance, absorbance, acidity and alkalinity

6.2.1.1. 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 polyvinyl 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.

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 withstand the stresses 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

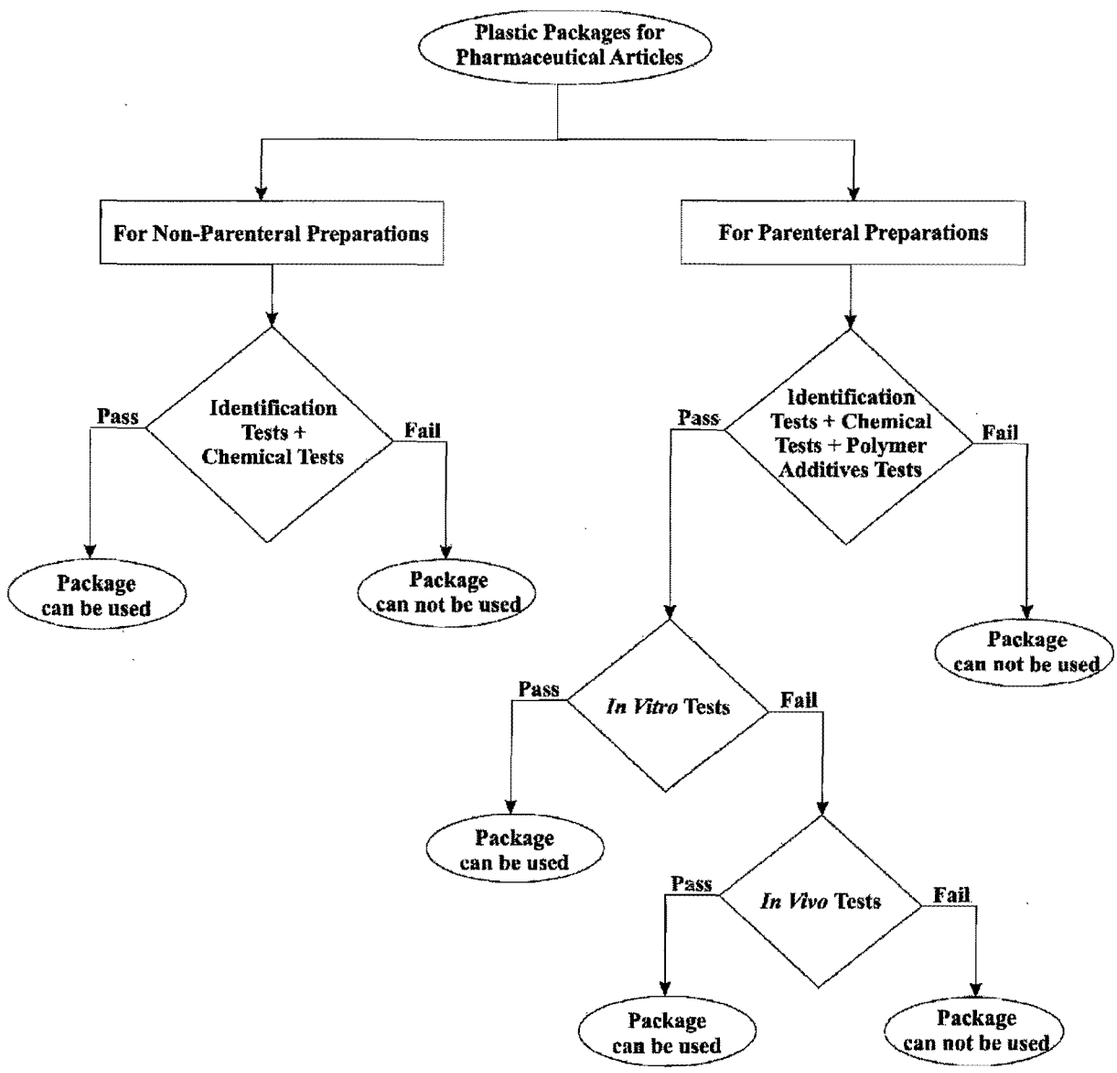


Fig. - Approval Philosophy-Plastics for Pharmaceutical Packaging

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 stresses and rigors of transportation and packaging. The containers must withstand the sterilisation conditions to which they will be subjected. 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 them, 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.

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.

Visual inspection. The empty containers display no defects that may lead to leakage and the filled and closed container shows no leakage.

Tests on Containers

Leakage test. Fill ten containers with water, fit them 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 per cent of its nominal contents at the required rate of flow at ambient temperature.

*NOTE 4 — **Testing of Secondary Packages - Special Case***

For satisfactory storage of some preparations, the container needs to be enclosed in a protective envelope. In such cases, the initial evaluation of storage is carried out using the container enclosed in the envelope.

*NOTE 5— **Additional requirements on Plastic containers for Parenteral Preparations***

For Plastic Containers for Parenteral Preparations

a) Other suitable means of ensuring package integrity may also be used.

b) All considerations covered in details in the Plastic Containers for Non-parenteral Preparations (6.2.1.2) shall apply.

Tests using Special Solution "S"

Preparation of Special Solution "S"

Fill a container under examination to its nominal capacity with water and close it, using the usual means of closure; otherwise closed using a suitable sheet / foil of aluminium. Heat in an autoclave so that a temperature of 121± 2° is reached within 20 to 30 minutes and maintain at this temperature for 30 minutes. If heating at 121° leads to deterioration/deformation of the container, heat at 100° 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 an aluminium foil at the temperature and for the time used for the preparation of solution S.

Tests Using Solution "S"

Clarity and Colourof 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 per cent of the nominal capacity of the container add 0.1 ml of *phenolphthalein solution*. 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*. The solution is orange-red or red.

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

Reducing substances. To 20.0 ml of solution S add 1 ml of *dilute sulphuric acid* and 20.0 ml of *0.002 M potassium permanganate*. Boil for 3 minutes. Cool immediately. Add 1 g of *potassium iodide* and titrate immediately with *0.01 M sodium thiosulphate*, using 0.25 ml of *starch solution* as indicator.

Carry out a titration using 20.0 ml of the blank prepared as described under Solution S.

The difference between the titration volumes is not more than 1.5 ml.

Transparency. Fill the containerpreviously used for the preparation of solution Sto its nominal capacity with a 1 in 200 dilution of the standard suspension (2.4.1) when made from polyethylene or polypropylene. For containers made of other plastics, use a 1 in 400 dilution.

The cloudiness of the suspensionis perceptible when viewed through the container and compared with a similar container filled with *water* (2.4.1).

6.2.1.1.1. 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 (6.2.1.1).

Materials other than those described in this 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 Blood and Blood Components.

In normal conditions of use the plastic 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 phlebotomicneedle 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/appendage for continuous flow which does not hinder the collection, storage, processing or administration of the blood.

The containers are enclosed in sealed, protective envelopes (See NOTE 4).

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 5.0 ml of air.

Tests

Solution S1. Fill the container with 100.0 ml of 0.9 per cent w/v solution of sodium chloride. Close the container and heat it in an autoclave so that the contents are maintained at 110° for 30 minutes.

If the container under examination contains an anticoagulant solution, first empty it, rinse the container with 250.0 ml of *water for injections* at 20 ± 1° 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° 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 1 ml 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 1 ml of *dilute hydrochloric acid,* sufficient to fill it to its nominal capacity. Send the container by the sending 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 0.9 per cent w/v solution of sodium chlorideequal to the volume of blood for which the container is intended.

For an empty container, fill with the same mixture of anticoagulant solution and 0.9 per cent w/v solution of sodium chloride. Close the container, weigh it and store it at 5 ± 1° in an atmosphere with a relative humidity of 50 ± 5 per cent for 21 days.

At the end of this period the loss in weight is not more than 1 per cent.

Emptying under pressure. Fill the container with a volume of *water* at 5 ± 1° 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 per cent w/v solution of *sucrose* at 37°. 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° to 23°. Cool it rapidly in a deep-freezer to –80° and maintain it at this temperature for 24 hours. Raise the temperature to 50° 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, Emptyingunder 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 640 nm 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 elutes 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 90.0 g of *sodium chloride*, 34.6 g of *sodium phosphate* and 2.4 g of *sodium dihydrogen phosphate dihydrate* in *water* and dilute to 1000ml with the same solvent. Prepare three buffer solutions as follows

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

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

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

Introduce 1.4 ml of solution S2 into each of three centrifuge tubes. To tube I add 0.1 ml of buffer solution Ao, to tube II add 0.1 ml of buffer solution Bo and to tube III add 0.1 ml of buffer solution Co. To each tube add 0.02 ml of fresh, heparinised human blood, mix well and warm on a water-bath at 30±1° for 40 minutes. 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:

— 3.0 ml of buffer solution Ao and 12.0 ml of *water* (solution A1),

— 4.0 ml of buffer solution Bo and 11.0 ml of *water* (solution B1),

— 4.75 ml of buffer solution Bo and 10.25 ml of *water* (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 S2 by *water*.

Centrifuge simultaneously the tubes to be examined and the control tubes at exactly 2500 g 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

$$\frac{A_{exp}}{A_{100}} \times 100$$

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 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. Introduce aseptically into the container 100.0 ml of 0.9 per cent w/v solution of sodium chlorideand 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 S1complies with the test for pyrogens (2.2.8). Inject 10.0 ml of the solution per kilogram of the rabbit's weight.

Abnormal toxicity. Solution S1 complies with the general test for abnormal toxicity (2.2.1). Inject 0.5 ml of the solution into each mouse.

Containers and Closures. Sterile plastic containers for human blood and blood components are packed in protective tamper-evident envelopes. On removal from its protective envelope thecontainer 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 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.

6.2.1.1.2.Sterile PVC (Polyvinyl chloride) Containers for Blood and Blood Components

Sterile PVC (Polyvinyl chloride) containers for blood and blood components should meet the requirements described under the introductory part of section 6.2.1.of chapter 6.2. 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*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* to fill the container to its nominal capacity (solution A). To a volume of solution A corresponding to 4 per cent of the nominal capacity of the container add 0.1ml of *phenolphthalein solution;* the solution remains colourless.

Add 0.4 ml of *0.1 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;* the solution is orange-red or red.

Light absorption. Heat *water* in a round bottom flask in an autoclave at 110° for 30 minutes (solution B). Measure the light absorption of solution A in the range 230 nm to 360 nm using solution B as blank.

The absorbance is not more than 0.30 at any wavelength from 230 nm to 250 nm and not more than 0.10 at any wavelength from 251 nm to 360 nm (2.4.7).

Ammonium. Dilute 5.0 ml of solution A to 14.0 ml with *water* in a test-tube, if necessary make alkaline with *2 M sodium hydroxide* and dilute further to 15.0 ml with *water.* Add 0.3 ml of *alkaline potassium mercuric-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 10.0 ml of *ammonium standard solution (1 ppm NH4)* and 5.0 ml of *water* in the samemanner (2 ppm).

Chlorides. 15.0 ml of solution A complies with the limit test for chlorides (2.3.12). Prepare the standard using a mixture of 1.2 ml of *chloride standard solution (5ppm Cl)* and 13.8 ml 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 0.1 g of *di(2-ethylhexyl)phthalate* in the extraction solvent and dilute to 100.0 ml with the same solvent.

Standard solutions

(a) Dilute 20.0 ml of stock solution to 100.0 ml with extraction solvent.

(b) Dilute 10.0 ml of stock solution to 100.0 ml with extraction solvent.

(c) Dilute 5.0 ml of stock solution to 100.0 ml with extraction solvent.

(d) Dilute 2.0 ml of stock solution to 100.0 ml with extraction solvent.

(e) Dilute 1.0 ml of stock solution to 100.0 ml with extraction solvent.

Measure the absorbance of the standard solutions at the maximum at about 272 nm, 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° 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° 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 272 nm, using the extraction solvent as blank (2.4.7).

Determine the concentration of di(2-ethylhexyl)phthalate in milligrams/100.0 ml of the extract from the calibration curve. The concentration does not exceed

— 10.0 mg per 100.0 ml for containers of nominal volume greater than 300 ml but not greater than 500 ml;

— 13.0 mg per 100.0 ml for containers of nominal volume greater than 150 ml but not greater than 300 ml;

— 14.0 mg per 100.0 ml for containers of nominal volume upto 150 ml.

Oxidisable substances. Immediately after preparation of solution A, 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 solution B in another borosilicate-glass flask. To each solution add 20.0 ml of *0.002 M potassium permanganate* and 1ml of *1 M sulphuric acid.* Allow to stand at room temperature, protected from light, for 15 minutes. To each solution add 0.1 g of *potassium iodide.* Allow to stand protected from light for 5 minutes and titrate immediately with *0.01 M sodium thiosulphate,* using 0.25 ml of *starch solution* as indicator.

The difference between the two titrations is not more than 2.0ml.

Residue on evaporation. Evaporate to dryness 100.0 ml of solution A in a borosilicate-glass beaker, previously heated to 105°. Evaporate to dryness in the same conditions 100.0 ml of solution B. Dry to constant weight at 105°.

The difference between the weights of the residues is not more than 3mg.

6.2.1.1.3. Sterile PVC (Polyvinyl chloride) Containers for Blood containing an Anticoagulant Solution

Unless otherwise authorised as described in the introductory part of section 6.2.1 under Containers (6.2.), the nature and composition of the material from which the containers are made complies with the requirements described under Sterile PVC (Polyvinyl chloride) containers for blood and blood components (6.2.1.1.2.).

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 Sterile PVC (Polyvinyl chloride) containers for blood and blood components (6.2.1.1.2.).

After addition of the anticoagulant solution the containers comply with the tests described under Sterile Plastic Containers for Blood and Blood Components (6.2.1.1.1.) 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 350 nm 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 280 nm 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 Sterile PVC (Polyvinyl chloride) containers for blood and blood components (6.2.1.1.2).

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

6.2.1.2. Plastic Containers for Non-parenteral Preparations

Tests on Containers

The container used for packaging of pharmaceutical formulations shall meet all the test requirements detailed below.

Leakage test, Collapsibility test. Comply with the tests described under Plastic Containers for Parenteral Preparations (6.2.1.1.).

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 20 cm^2. 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 1250 cm^2, transfer to a flask, previously cleaned with *chromic acid mixture* and rinsed with several portions of *distilled water* and add 250 ml of *distilled water*. Cover the flask with a beaker and autoclave at 121° for 30 minutes. Carry out a blank determination using 250 ml of *distilled water*.

Cool and examine the extract; it is colourless and free from turbidity.

Non-volatile residue. Evaporate 100.0 ml of the extract obtained in the test for Clarity of aqueous extract to dryness and dry to constant weight at 105°.

The residue weighs not more than 12.5 mg.

Tests on Container Materials

*NOTE 6 — **Requirements for test specimens***

a) on portions of the container that are unlabelled, unprinted or non-laminated or

b) on the granules of plastic in the case of containers made by the 'form-fill-seal' process.

*NOTE 7 —**Regarding testing of extractable metals***

a) For quantitative determination of the extractable metals described hereunder, Inductively Coupled Plasma Mass Spectrometry (ICP-MS) (2.4.42) may be used. Alternatively, Atomic Absorption Spectrometry (AAS) (2.4.2) can be used provided it has the appropriate sensitivity.

b) Extractable metals are measured using special solutions as described under each plastic container.

c) Permissible limits mentioned in the paragraphs below are extractable metals in the Plastics. These have been expressed as ppm (µg of extracted metal per g of Plastics in the special solutions, after appropriate calculations).

d) The extractable elements described herein for estimation are based on their historical presence in the manufacturing processes for each plastic. Additional elements, if used by any manufacturer, should be suitably estimated.

6.2.1.2.1. Polyethylene Terephthalate (PET) Containers

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 per cent 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° and high vacuum. The manufacturing process of the PET pellets (resin) shall ensure that the residual acetaldehyde content is not greater than 10 ppm.

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 colourants conforming to Indian Standards IS-9833 and/or additives conforming to IS-12252.

The manufacturers of containers should receive the certificate of analysis for each lot of resins procured from to confirm the quality of resins that the grade of resins used is as agreed and meets the relevant specification. The certificate of analysis from the resin manufacturer shall provide the necessary assurance about the quality of resin.

Quality assessment of PET Containers

The container used for packaging of pharmaceutical formulations shall meet all the test requirements detailed below.

A. IDENTIFICATION OF CONTAINER MATERIAL

Test 1 – By FTIR Spectrophotometry

Dissolve 50mg of the PET container specimen under examination in 2 ml of solvent blend of *phenol* and *tetrachloroethane* (60:40 *w/w)*with heating followed by centrifugingor *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 15 mm by 15 mm. 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° for about 1 hour).

Examine the film by infrared absorption spectrophotometry (2.4.6). The spectrum should show absorption maxima substantially at about 3053 cm^{-1}, 1955 cm^{-1}, 1725 cm^{-1}, 1613 cm^{-1}, 1455 cm^{-1},1410 cm^{-1}, 1265 cm^{-1}, 1020 cm^{-1}, 973 cm^{-1}, 875 cm^{-1}, and 730 cm^{-1}.

NOTE—Substantial, as opposed to exact, allows for minor spectral differences arising from the natural compositional and/or physical variation and/or instrumental capabilities.

Test 2 – By UV Spectrophotometry

Reflux 100.0 mg of the PET container under examination with 25.0 ml of a 20 per cent *w/v* solution of *potassium hydroxide* in a 50 per cent v/v solution of *ethanol* for 30 minutes in a round bottom flask. Allow to cool and dilute to 100.0 ml with *water*. Filter if necessary. Dilute 1.0 ml of the filtrate to 100.0 ml with *water*.

Examine this solution in the range 210 nm and 330 nm (2.4.7), the absorption maximum should be at about 240 nm.

Test 3 – By Differential Scanning Calorimetry (2.4.31)

Conduct the entire test under nitrogen. Heat the specimen from room temperature to 290° at a heating rate between10 and 20°/minute and hold it for 1 minute. Cool the specimento room temperature at the highest cooling rate possible (typically, lower than a rate of 50° per minute) and hold it for 1 minute. Reheat it to 290° at the same rate as adopted in the first heating.This reheats thermogram to be used for comparison.

Compare the thermogram of the sample with that of the reference PET. The melting peak temperature obtained from the thermogram of the sample does not differ from that of the reference thermogram by more than 8.0°.

B. CHEMICAL TESTS

B1. Tests using special solutions

Preparation of Special Solutions for Subsequent Tests on PET

Select required quantity of unlabelled, unmarked and non-laminated portions from suitable containers, taken at random. Cut them into pieces each having an area not more than 1 cm^2.

Solution S1 (Water Extraction)

Place 10 g of the sample in a round bottom flask. Add 200.0 ml of *water* and heat at 50° for 5 hours. Allow to cool and then decant the solution.

NOTE— Use solution S1 within 4 hours of its preparation.

Solution S2 (Ethanol Extraction)

Place 10 g of the sample in a round bottom flask. Add 100.0 ml of *ethanol (95* per cent*)*and reflux at 50° for 5 hours. Allow to cool and decant the solution.

NOTE— Use solution S2 within 4 hours of its preparation.

Solution S3 (Acid Extraction)

Place 20 g of the sample in a round bottom flask. Add 50.0 ml of *0.1 M hydrochloric acid* and heat at 50° for 5 hours. Allow to cool and decant the solution.

NOTE— Use solution S3 within 4 hours of its preparation.

Solution S4 (Alkali Extraction)

Place 20 g of the sample into a round bottom flask. Add 50.0 ml of *0.01 M sodium hydroxide* and heat at 50° for 5 hours. Allow to cool and decant.

Use solution S4 within 4 hours of its preparation.

Tests using the Special Solution S1

B1.1. Appearance

Solution S1 has to be clear (2.4.1).

B1.2. Absorbance of solution S1 (2.4.7)

— In the UV- range (220 nm to 340 nm): absorbance should be not more than 0.20

— In the visible range (400 nm to 800 nm): absorbance should be not more than 0.05

B1.3. Acidity

To 50.0 ml of solution S1 add 0.15 ml of *BRP indicator solution.* The solution turns yellow. Not more than 0.5 ml of *0.01 M sodium hydroxide* is required to change the colour of the indicator to blue.

B1.4. Alkalinity

To 50.0 ml of solution S1, add 0.2 ml of *methyl orange solution.* The solution turns yellow.

Not more than 0.5 ml of *0.01M hydrochloric acid* is required to reach the beginning of the colour change of the indicator to orange.

B1.5. Reducing substances

To 20.0 ml of solution S1, add 2.0 ml of *0.5 M sulphuric acid* and 20.0 ml of *0.002 M potassium permanganate*. Boil for 3 minutes. Immediately cool to room temperature. Add 1.0 g of *potassium iodide*, 0.25 ml of *starch solution* as indicator and titrate with *0.01 M sodium thiosulphate*. Perform a blank titration using 20.0 ml of *water*.

The difference in volume used in the 2 titrations is not greater than 0.5 ml.

Tests using the Special Solution S2

B1.6. Appearance

Solution S2 has to be clear and colourless (2.4.1).

B1.7. Absorbance of solution S2 (2.4.7)

In the visible range (400 nm to 800 nm): absorbance should be not more than 0.05.

B1.8. Extractable Metals

Tests using the Special Solution S3

B1.8.1. Aluminium. Not more than 1 ppm.

Reference solutions. Prepare the suitably diluted solutions from reference standard solutions of *aluminium (200 ppm Al)* with *0.1 M hydrochloric acid.*

Wavelength. 396.15 nm, the spectral background being taken at 396.25 nm.

Verify the absence of aluminium in the *0.1 M hydrochloric acid* used.

B1.8.2. Barium. Not more than 1 ppm.

Reference solutions. Prepare the suitably diluted solutions from reference standard solutions of *barium (50 ppm Ba)* with *0.1 M hydrochloric acid.*

Wavelength. 455.40 nm, the spectral background being taken at 455.30 nm.

Verify the absence of barium in the *0.1 M hydrochloric acid* used.

B1.8.3. Cobalt. Not more than 1 ppm.

Reference solutions. Prepare the suitably diluted solutions from reference standard solutions of *cobalt (100 ppm Co)* with *0.1 M hydrochloric acid.*

Wavelength. 228.62 nm, the spectral background being taken at 228.50 nm.

Verify the absence of cobalt in the *0.1 M hydrochloric acid* used.

B1.8.4. Manganese. Not more than 1 ppm.

Reference solutions. Prepare the suitably diluted solutions from reference standard solutions of *manganese (100 ppm Mn)* with *0.1 M hydrochloric acid.*

Wavelength. 257.61 nm, the spectral background being taken at 257.50 nm.

Verify the absence of manganese in the *0.1 M hydrochloric acid* used.

B1.8.5. Titanium. Not more than 1 ppm.

Reference solutions. Prepare the suitably diluted solutions from reference standard solutions of *titanium (100 ppm Ti)* with *0.1 M hydrochloric acid.*

Wavelength. 323.45 nm or 334.94 nm, the spectral background being taken at 323.35 nm.

Verify the absence of titanium in the *0.1 M hydrochloric acid* used.

B1.8.6. Zinc. Not more than 1ppm.

Reference solutions. Prepare the suitably diluted solutions from reference standard solutions of *zinc (100 ppm Zn)* with *0.1 M hydrochloric acid.*

Wavelength. 213.86 nm, the spectral background being taken at 213.75 nm.

Verify the absence of zinc in the *0.1 M hydrochloric acid* used.

Tests using the Special Solution S4

B1.8.7. Antimony. Not more than 1 ppm.

Reference solutions. Prepare suitably diluted solutions from the reference standard solutions of *antimony (100 ppm Sb)* with *0.01 M sodium hydroxide.*

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

B2. Related Substances (Residual Monomers/Residual Inoroganics)

B2.1. Substances soluble in dioxane

Place 2.0 g of the material to be examined in a round bottom flask. Add 20.0 ml of *dioxane* and heat under reflux for 2 hours. Filter the solution. Take 10.0 ml from filtrate and evaporate to dryness on a water-bath and then dry the residue at 100-105°

The residue weighs a maximum of 30.0 mg.

B2.2. Sulphated ash (2.3.18). Not more than 0.5 per cent determined on 1.0 g.

B2.3. Total Terephthaloyl moieties. Not more than 1 ppm

Polyethylene terephthalate extracting media.(1) 50 per cent *ethanol* (dilute 125 ml of *ethanol (95 per cent)*, with *Purified Water* to 238.0 ml, and mix), (2) *n-heptane* and (3) *water.*

For each extracting media fill a sufficient number of test containers to 90 per cent of its nominal capacity to obtain not less than 30.0 ml.

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° 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 per cent ethanol extract at the wavelength of maximum absorbance at about 244 nm (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 240 nm (2.4.7). For the blank use corresponding extracting medium blank.

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

B2.4. Ethylene glycol. Not more than 1 ppm.

Periodic acid solution. Dissolve 125 mg of periodic acid in 10.0 ml of *water.*

Dilute sulphuric acid. To 50.0 ml of *water*, slowly add and with constant stirring 50.0 ml of *sulphuric acid*, allow to cool to room temperature.

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 of fume hood is recommended.

Sodium bisulphite solution. Dissolve 100 mg of *sodium bisulphite* in 10.0 ml of *water.*

Disodium chromotropate solution. Dissolve 100 mg of *disodium chromotropate* in 100.0 ml of *sulphuric acid.*

Reference solution. Dissolve quantity of ethylene glycol in the *water*, to obtain a solution containing 0.0001 per cent w/v of ethylene glycol.

Test solution. Use the water extract from Total Terephthaloyl moieties

Procedure. Transfer 1.0 ml of the reference solution, test solution and purified water extracting medium in three separate volumetric flasks. Add 0.1 ml of *periodic acid solution* to each flask swirl to mix, and allow to stand for 60 minutes. Add 1.0 ml of *sodium bisulphite solution* to each flask, and mix. Add 0.1 ml of *disodium chromotropate solution* to each flask, and mix.

(*NOTE*—All the solutions should be analysed within 1 hour after addition of *disodiumchromotropate solution*) Slowly add 6.0 ml 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 575 nm (2.4.7), using *water extracting medium* as the blank.

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

6.2.1.2.2. Polyethylene (HDPE and LDPE) Containers

Polyethylene is manufactured by addition polymerization of ethylene(C_2H_4), in the gas phase.The two most common types of polyethylene are high density polyethylene (HDPE) and low density polyethylene (LDPE).

Production of Polyethylene

HDPE is manufactured at pressures as low as 5 bar and low temperatures typically below 90°, using Ziegler-Natta and activated chromium oxide (known as a Phillips catalyst). The plastic identification code of HDPE is 2.

LDPE is prepared from gaseous ethylene under very high pressures upto 2500 bar andtemperatures upto 320°. These processes yield a polymer structure with both long and short branches. The plastic identification code of LDPE is 4.

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

The resin and its conversion into containers may involve the use of colourants conforming to Indian Standards IS-9833 and/or additives conforming to IS-10141.

The manufacturers of containers should receive the certificate of analysis for each lot of resins procured from to confirm the quality of resins that the grade of resins used is as agreed and meets the relevant specification. The certificate of analysis from the resin manufacturer shall provide the necessary assurance about the quality of resin.

A. Identification of Container Material

High-density polyethylene

Test 1 – By FTIR Spectrophotometry (2.4.6)

Determine the infrared spectrum from 4400 cm^{-1} to 650 cm^{-1}. The specimen exhibits an absorption spectrum that is substantially equivalent to that of High-Density *Polyethylene*. Substantial, as opposed to exact, equivalence allows for minor spectral differences arising from the natural compositional and/or physical variation among polymers of this class. Substantial equivalence is achieved when all differences between the sample and reference spectra can be explained in the context of such natural compositional and/or physical variations.

Test 2 – By Differential Scanning Calorimetry (2.4.31)

Place about 12 mg of sample in the test specimen pan. [Note – Intimate contact between the pan and the thermocouple is essential for obtaining reproducible results]. Determine the thermogram under nitrogen, using heating/cooling conditions specified for the polymer type and using equipment capable of performing the determinations. Thermogram are obtained for the test materials and their associated reference standards.

Conduct the entire test under nitrogen. Heat the specimen from 40° to 200° at a heating rate between 2° and 10°/minute and hold it for 1 minute. Cool the specimento 40° at the same rate adopted for heatingand hold it for 1 minute. Reheat it to 200° at the same rate.This reheats thermogram to be used for comparison.

Compare the thermogram of the specimen with that of the reference HDPE. The melting peak temperature obtained from the thermogram of the specimen does not differ from that of the reference thermogram by more than 6.0°.

Low-density polyethylene

Test 1 – By FTIR Spectrophotometry (2.4.6)

Determine the infrared spectrum from 4400 cm^{-1} to 650 cm^{-1}. The specimen exhibits an absorption spectrum that is substantially equivalent to that of the Low-Density *Polyethylene*. Substantial, as opposed to exact, equivalence allows for minor spectral differences arising from the natural compositional and/or physical variation among polymers of this class. Substantial equivalence is achieved when all differences between the sample andreferencespectra can be explained in the context of such natural compositional and/or physical variations.

Test 2 – By Differential Scanning Calorimetry (2.4.31)

Method is same as for HDPE.

Conduct the entire test under nitrogen. Heat the specimen from 40° to 200° at a heating rate between 2° and 10°/minute and hold it for 1 minute. Cool the specimento 40° at the same rate adopted for heatingand hold it for 1 minute. Reheat it to 200° at the same rate.This reheats thermogram to be used for comparison.

Compare the thermogram of the specimen with that of the reference LDPE. The melting peak temperature obtained from the thermogram of the specimen does not differ from that of the reference thermogram by more than 8.0°.

B Chemical Tests

Preparation of Special Solutions for subsequent tests on Polyethylene

Solution S1 (Water extraction)

Place 25 g of the test material in a borosilicate glass flask with a ground-glass neck. Add 500 ml of purified water, and boil under reflux conditions for 5 hours. Allow to cool to ambient temperature, and filter the extracting solution through a sintered-glass filter. Collect the filtrate in a 500 ml volumetric flask and dilute with purified water to volume; the diluted solution is *Solution S1*.

Use Solution S1 within 4 hours of preparation.

Solution S2 (Toluene extraction)

Place 2.0 g of the test material in a 250 ml borosilicate glass flask with a ground-glass neck. Add 80 ml of *toluene* and boil under a reflux condenser for 1.5 hours, stirring constantly. Allow to cool to 60° and add 120.0 ml of methanol with continued stirring. Pass the resulting solution through a sintered-glass filter. Rinse the flask and the filter with 25.0 ml of a mixture of 40 volumes of *toluene* and 60 volumes of *methanol* add the rinsing to the filtrate, and dilute to 250 ml with the same mixture of solvents to produce *Solution S2*. Prepare a blank solution.

Solution S3 (Acid extraction)

Place 5.0 g in a borosilicate glass flask with a ground-glass neck. Add 100.0 ml of *0.1 M hydrochloric acid*, and boil under a reflux condenser for 1 hour with constant stirring. Allow to cool and the solids to settle,decant the solution into a 100.0 ml volumetric flask, and dilute to volume with *0.1 M hydrochloric acid*; the diluted solution is *Solution S3*.

Tests Using Special Solutions

B.1. Absorbance (2.4.7)

Determine the spectrum between 220 nm and 340 nm in Solution S1.

Absorbanceshould be not more than 0.2

B.2. Acidity or alkalinity

To 100.0 ml of Solution S1 add 0.15 ml of *BRP indicator solution*. Determine the titration volume of *0.01M sodium hydroxide* required to change the colour of the indicator to blue. To a separate, 100.0 ml portion of Solution S, add 0.2 ml of *methyl orange solution*. Determine the titration volume of *0.01 M hydrochloric acid* required to reach the beginning of the colour change of the indicator from yellow to orange.

Not more than 1.5 ml of *0.01 N sodium hydroxide* is required to change the colour of the indicator to blue. Not more than 1.0ml of *0.01N hydrochloric acid* is required to reach the beginning of the colour change of the indicator from yellow to orange.

B.3. Polymer Additives

These tests should be carried out in whole or in part as required due to the stated composition of the material.

B.3.1. Phenolic Antioxidant

Solvent mixture.Mixture of equal volumes of *acetonitrile*and *tetrahydrofuran*.

Sample solution S2A. Evaporate 50.0 ml of Solution S2 to dryness under vacuum at 45°. Dissolve the resulting residue with 5.0 ml of the solvent mixture. Prepare a blank solution from the blank solution corresponding to Solution S2.

Sample solution S2B. Evaporate 50.0 ml of Solution S2 to dryness under vacuum at 45°. Dissolve the residue with 5.0 ml of *methylene chloride*. Prepare a blank solution from the blank solution corresponding to Solution S2.

Of the following reference solutions; prepare only those that are necessary for the analysis of the phenolic antioxidants stated in the composition of the substance to be examined.

Reference solution (a). A 0.01 per cent w/v of *butylated hydroxytoluene RS* and 0.024 per cent w/v of *polymer additive 01 RS* in the solvent mixture.

Reference solution (b). A 0.024 per cent w/v of *polymer additive 02 RS* and 0.024 per cent of *polymer additive 03 RS* in the solvent mixture

Reference solution *(c)*. A 0.024 per cent of *polymer additive 04 RS* and 0.024 per cent of *polymer additive 05 RS* in *methylene chloride*

Reference solution (d). A 0.01 per cent of *butylated hydroxytoluene RS* in the solvent mixture

Reference solution (e). A 0.024 per centof *polymer additive 01 RS* in the solvent mixture

Reference solution (f). A 0.024 per cent of *polymer additive 06 RS* prepared in the solvent mixture

Reference solution (g). A 0.024 per cent of *polymer additive 02 RS* prepared in the solvent mixture

Reference solution (h). A 0.024 per cent of *polymer additive 03 RS* prepared in the solvent mixture

Reference solution (i). A 0.024 per cent of *polymer additive 04 RS* prepared in *methylene chloride*

Reference solution (j). A 0.024 per cent of *polymer additive 05 RS* prepared in *methylene chloride*

Test A

Determine by liquid chromatography (2.4.14).

If the substance to be examined contains additive butylatedhydroxytoluene and/or additive ethylene bis[3,3-bis[3-(1,1dimethylethyl)-4-hydroxyphenyl]butanoate

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica microparticles (5µm),
- mobile phase: a mixture of 70 volumes of a *acetronitrile* and 30 volumes of *water*,
- flow rate: 2.0 ml perminute,
- spectrophotometer set at 280 nm,
- injection volume: 20 µl.

Inject reference solution (a). The test is not valid unless the resolution between the peaks due to additive butylatedhydroxytolueneand additive ethylene bis[3,3-bis[3-(1,1-dimethylethyl)-4-hydroxyphenyl]butanoate] peaks is not less than 8.0.

Inject Sample solution S2A, corresponding blank solution, and Reference solution (d), Reference solution (e), or both. Run the chromatogram for about 30 minutes.

The peak areas of Sample solution S2A are less than the corresponding peak areas of Reference solution (d) or Reference solution (e).

NOTE— Sample solution S2A shows only peaks caused by antioxidants stated in the composition and minor peaks that also correspond to the blank solution.

Test B

If the substance to be examined contains one or more of the following antioxidants pentaerythritoltetrakis[3-(3,5-di tert-butyl-4-hydroxyphenyl)propionate; 2,2,23 ,6,6,63 -hexa-tert-butyl-4,4,43 -[(2,4,6-trimethyl-1,3,5-benzene-triyl)tris-methylene]triphenol; octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate; tris(2,4-di-tert-butylphenyl) phosphite; 1,3,5-tris(3,5-di-tert-butyl-4-hydroxybenzyl)-s-triazine-2,4,6(1*H*,3*H*,5*H*)-trione

Determine by liquid chromatography(2.4.14).

Chromatographic system

Carry out the test as described in Test A with the following modifications

- mobile phase: a mixture of 60 volumes of *acetronitrile* 30 volumes of *tetrahydrofuran* and 10 volumes of *water,*
- flow rate: 1.5 ml per minute.

Inject reference solution (b).The test is not valid unless the resolution between the peaks due to additive pentaerythritoltetrakis[3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionate and additive 2,2',23 ,6,6',63 -hexa-tert-butyl-4,4',43 -[(2,4,6-trimethyl-1,3,5-benzene-triyl)trismethylene]triphenol is not less than 2.0.

Inject Sample solution S2A, corresponding blank solution and any Reference solutions of the antioxidants listed above that are stated in the composition. The peak areas of Sample solution S2A are less than the corresponding peak areas of Reference solutions of the antioxidants that are listed above and that are stated in the composition.

NOTE— Sample solution S2A shows only peaks caused by antioxidants stated in the composition and minor peaks that also correspond to the blank solution.

Test C

If the substance to be examined contains additive octadecyl-3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate and/or additive tris(2,4-di-tert-butylphenyl) phosphite.

Determine by liquid chromatography (2.4.14).

Chromatographic system

Carry out the test as described in Test A with the following modifications

- mobile phase: a mixture of 50 volumes of *methanol*, 45 volumes of 2 *propanol* and 5.0 volumes of *water*,
- flow rate: 1.5 ml per minute.

Inject reference solution (c).The test is not valid unless the resolution between the peaks due to additive octadecyl-3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate and additive tris(2,4-di-tert-butylphenyl) phosphite is not less than 2.0.

Inject Sample solution S2B, corresponding blank solution, and either Reference solutions (i) or reference solution (j) of the antioxidants listed above that are stated in the composition. The peak areas of Sample solution S2B are less than the corresponding peak areas of Reference solutions of the antioxidants that are listed above and that are stated in the composition.

NOTE—Sample solution S2B shows only peaks caused by antioxidants stated in the composition and minor peaks that also correspond to the blank solution.

B.3.2. Non-phenolic Antioxidant

Determine by thin-layer chromatography(2.4.17), using the plate coated with *silica gel GF254.*

Mobile phase A. Hexane.

Mobile phase B. Methylene chloride.

Methylene chloride, acidified. To 100.0 ml of *methylene chloride* add 10.0 ml of *hydrochloric acid*, shake, allow to stand, and separate the two layers. Use the lower layer.

Sample solution S2C. Evaporate 100.0 ml of Solution S2 to dryness under vacuum at 45°. Dissolve the resulting residue with 2ml of *methylene chloride* acidified.

Reference solution (m). A 0.6 per cent w/v of *polymer additive 08 RS* in *methylene chloride*. Dilute 2 ml of the solution with *methylene chloride*, acidified to 10 ml.

Reference solution (n). A 0.6 per cent w/v of *polymer additive 09 RS* in *methylene chloride*. Dilute 2 ml of the solution with *methylene chloride*, acidified to 10.0 ml.

Reference solution (o). A 0.6 per cent w/v of *polymer additive 10 RS* in *methylene chloride*. Dilute 2 ml of the solution with *methylene chloride*, acidified to 10.0 ml.

Reference solution (p). A 0.6 per cent of *polymer additive 10 RS*, and 0.6 per cent of *polymer additive 09 RS* in *methylene chloride*. Dilute 2 ml of the solution with *methylene chloride*, acidified to 10.0 ml.

Apply to the plate 20 µl of sample solution S2C, reference solution (p) and the reference solutions corresponding to all the phenolic and non-phenolic antioxidants expected to be present. Develop the plates over a path of 18 cm with Mobile phase A,dry in air, again develop the plate over a path of 17 cm with Mobile phase B and dry in air. Spray with alcoholic iodine solution, allow to stand for 10 to 15 minutes and examine under ultraviolet light at 254 nm.

The test is not valid unless the chromatogram obtained with reference solution (p) shows two separate spot. Any spot in the chromatogram obtained with sample solution S2C is not more intense than the spot in the same position in the chromatogram of the corresponding reference solution.

B.3.3. Amides and Stearates

Use sample solution as sample solution S2C as described in Non-phenolic Antioxidants.

Reference solution (r). A 0.2 per cent of *stearic acid RS* prepared in *methylene chloride.*

Reference solution (s). A 0.2 per centof *polymer additive 12 RS* prepared in *methylene chloride.*

Reference solution (t). A 0.2 per cent of *polymer additive 13 RS* prepared in *methylene chloride.*

Test A

Determine by thin-layer chromatography(2.4.17), using the plate coatedwith silica *gel GF254*

Mobile phase. a mixture of 75 volume of *trimethylpentane*and 25 volumes of *alcohol.*

Apply to the plate 10 µl of sample solution S2C and reference solution (r). Develop the plate over a path of 10 cm with mobile phase. After development, dry the plate in air, spray with 2 per cent 2,6-dichlorophenol-indophenol sodium in dehydrated alcohol, heat in an oven at 120° for a few minutes to intensify the spots and examine any spot corresponding to additive stearic acid in the chromatogram obtained with sample solution S2C (R_f= about 0.5) is not more intense than the spot in the same position in the chromatogram of reference solution (r).

Test B

Determine by thin-layer chromatography (2.4.17), using the plate coated with *silica gel GF254.*

Mobile phase A. *Hexane*

*Mobile phase B.*A mixture of 95 volumes of *methylene chloride* and 5.0 volumes of *methanol.*

Apply to the plate 10 µl of sample solution S2C, reference solution (s) and reference solution (t). Develop the plateover a path of 13 cm with Mobile phase A andover a path of 10cm with Mobile phase B respectively. After each development, dry the plate in air and examine by spray with 40 per cent *phosphomolybdic acid* in *alcohol,* heat in an oven at 120° for a few minutes to intensify the spots and examineany spot corresponding to additive oleamide or erucamide in the chromatogram obtained with sample solution S2C (R_f= about 0.2) is not more intense than the spot in the same position in the chromatogram of reference solution (s) and reference solution (t).

B.4. Total organic carbon

The total organic content of Solution S1 is measured according to the general methodologies outlined in Total Organic Carbon (2.4.30).

The method used to perform the total organic carbonanalysis should have a limit of detection of 0.2 mg per litre (ppm) and should have a demonstrated linear dynamic range from 0.2 to 20 mg per litre (which encompasses the total organic carbon limit). A linear range with a higher upper concentration can be used if linearity is established. If sample extracts exceed this upper linear range, they must be diluted appropriately for analysis.

The difference between the sample and blank total organic carbon concentrations is not more than 5 mg per litre.

B.5. Extractable Metals

Solution S3 is used for acid extractable metals.

Procedure for extract analysis

Instrumentation and methods are those specified in Elemental Impurities (2.3.13A)

Aluminium. Solution S3 contains not more than 0.4 mg per litre (ppm), corresponding to 1 µg per g.

Arsenic, cadmium, lead, mercury, cobalt, and nickel. Report the measured value in Solution S3 at values above 0.01 mg per litre (ppm), corresponding to 0.025 µg per g. If the measured values are below these values, report the result as less than 0.01 mg per litre (ppm), corresponding to less than 0.025 µg per g.

Chromium. Solution S3 contains not more than 0.02 mg per litre (ppm), corresponding to 0.05 µg per g.

Titanium. Solution S3 contains not more than 0.4 mg per litre (ppm), corresponding to 1 µg per g.

Vanadium. Solution S3 contains not more than 0.04 mg per litre (ppm), corresponding to 0.1 µg per g.

Zinc. Solution S3 contains not more than 0.4 mg per litre (ppm), corresponding to 1 µg per g.

Zirconium. Solution S3 contains not more than 0.04 mg per litre (ppm), corresponding to 0.1 µg per g.

6.2.1.2.3. Polyvinyl Chloride(PVC, Non-Plasticized) Containers

Polyvinyl Chloride is a polymer whose basic building blocks are Vinyl Chloride monomers. It is a Thermoplastic polymer.

Production of PVC

The manufacturing processes for PVC production include Suspension Polymerisation, Emulsion Polymerisation or bulk polymerisation.

The product of the polymerization process is unmodified virgin PVC. Before PVC can be made into finished products, it always requires conversion into a compound by the incorporation of additives.

PVC's major benefit is its compatibility with many different kinds of additives, making it a highly versatile polymer.

The resin and its conversion into containers may involve the use of colourants conforming to Indian Standards IS-9833 and/or additives conforming to IS-10148.

The manufacturers of containers should receive the certificate of analysis for each lot of resins procured from to confirm the

quality of resins that the grade of resins used is as agreed and meets the relevant specification. The certificate of analysis from the resin manufacturer shall provide the necessary assurance about the quality of resin.

A. Identification of Container Material

Test 1 – By FTIR Spectrophotometry (2.4.6)

Determine the infrared spectrum from 3800 cm^{-1} to 650 cm^{-1}. The specimen exhibits an absorption spectrum that is substantially equivalent to that of the *polyvinyl chloride, non-plasticized RS*. Substantial, as opposed to exact, equivalence allows for minor spectral differences arising from the natural compositional and/or physical variation among polymers of this class. Substantial equivalence is achieved when all differences between the sample andreferencespectra can be explained in the context of such natural compositional and/or physical variations.

Test 2 – By Differential Scanning Calorimetry (2.4.31)

Conduct the entire test under nitrogen. Heat the specimen from -20° to 120° at a heating rate between 2° and 10° per minutes. For protecting the instrument, rapidly cool the specimento room temperature.This thermogram is to be used for comparison.

Compare the thermogram of the specimen with that of the reference PVC, Non-plasticized. The glass transition temperature obtained from the thermogram of the specimen does not differ from that of the reference thermogram by more than 8.0°.

NOTE—The results of the DSC analysis are strongly dependent on the amount of plasticizer in the test article.

B. Chemical Tests

Preparation of Special Solutions for subsequent tests on Polyvinyl Chloride

Solution S1 (Water extraction)

Place 25 g of the test material into a borosilicate glass flask. Add 500 ml of purified water, cover the flask's neck with aluminium foil or a borosilicate beaker, and heat in an autoclave at 121 ± 2° for 20 minutes. Allow the solution to cool and the solids to settle, decant the solution into a 500 ml volumetric flask, and dilute with purified water to volume; the diluted solution is *Solution S1*.

Solution S2 (Tetrahydrofuran extraction)

Dissolve 5.0 g of the test material in 80.0 ml of *tetrahydrofuran*and dilute to a volume of 100.0 ml with the same solvent. Filter if necessary; the solution may remain opaque. Slowly and drop wise add 70 ml *ethanol* to 20.0 ml of this solution. Cool the mixture in ice for 1 hours. Filter or centrifuge the mixture, collecting residue A. Wash residue A with *ethanol*. Collect the washings and add them to the solution remaining after filtration or centrifugation. Transfer the solution to a 100.0 ml volumetric flask and dilute to volume with ethanol. This process produces *Solution S2*. Prepare a blank solution.

Solution S3 (Acid extraction)

Place 5 g in a borosilicate glass flask with a ground-glass neck. Add 100.0 ml of *0.1 M hydrochloric acid*, and boil under a reflux condenser for 1 hours with constant stirring. Allow to cool and the solids to settle, decant the solution into a 100.0 ml volumetric flask, and dilute to volume with *0.1 M hydrochloric acid*; the diluted solution is *Solution S3*.

Tests Using Special Solutions

B.1. Absorbance (2.4.7)

Evaporate 100.0 ml of Solution S1 to dryness. Dissolve the residue in 5.0 ml of hexane. If necessary, pass through a filter that has been previously rinsed with hexane. Determine the spectrum between 250 nm and 330 nm in the dissolved residue.

Polyvinyl chloride, non-plasticized contains 1-phenyleicosane-1, 3-dione for dry dosage forms for oral administration.

Dilute 1.0 volume of Solution S2 to 10 volumes with ethanol prior to measurement. In all other situations, analyse Solution S2 with no further preparation. Determine the spectrum between 250 and 330 nm in the dissolved residue

Absorbanceshould be not more than 0.25 for containers for non-injectable aqueous solutions.

Absorbanceshould be not more than 0.30 for containers for dry dosage forms for oral administration

B.2. Additivesand Stabilizers for Polymers

The supplier of the material must be able to provide sufficient compositional information to establish whether the material meets the specifications for additives and stabilizers.

B.2.1. Tin in Tin-Stabilized Materials

Reference solution U. 0.081 per cent of *polymer additive 18 RS* prepared in *tetrahydrofuran*. Dilute 20.0 ml to 100.0 ml with *ethanol*.

Test solution. In a test tube, add 0.1 ml of Solution S2, Add 0.05 ml of *1M hydrochloric acid*, 0.5 ml of *potassium iodide solution*, and 5.0 ml of *ethanol*. Mix thoroughly and wait for 5 minutes. Add 9 ml of *water* and 0.1 ml of a 5 g per litre solution of *sodium sulphite* and mix thoroughly.

Add 1.5 ml of *dithizone solution* freshly diluted 100-fold with *methylene chloride*, shake for 15 seconds and allow to stand for 2 minutes.

Standard solution. Use 0.1 ml of Reference solution U through the same procedure as the 0.1 ml of Solution S2.

Compare the violet colour in the lower layer of the Sample solution to the violet colour in the lower layer of the Standard solution. The colour in the Sample solution should not be as intense as the colour in the Standard solution.

Not more than 0.25 per cent w/v.

B.2.2. Tin in Non Tin-Stabilized Materials

Test solution. In a test tube, add 0.1 ml of Solution S2, Add 0.05 ml of *1Mhydrochloric acid*, 0.5 ml of *potassium iodide solution*, and 5.0ml of *ethanol*. Mix thoroughly and wait for 5 minutes. Add 9 ml of water and 0.1 ml of a 5g per litre solution of *sodium sulphide* and mix thoroughly.

If the solution is not colourless, add the sodium sulphate in 0.05 ml fractions

Add 1.5 ml of dithizone solution freshly diluted 100-fold with *methylene chloride*, shake for 15 seconds and allow to stand for 2 minutes.

Standard solution. Use 0.05 ml of reference solution U as per the same procedure as the 0.1 ml of Solution S2.

Compare the violet colour in the lower layer of the Sample solution to the violet colour in the lower layer of the Standard solution. The colour in the Sample solution should not be as intense as the colour in the Standard solution.

Not more than 25 µg per g (ppm).

B.3. Related Substances (Residual Monomers / Residual Solvents)

B.3.1. Vinyl Chloride

Determine by gas chromatography (2.4.13).

Test solution. Place 1.0 g of the test material in a 50.0 ml vial, and add 10.0 ml of the internal standard solution. Close the vial, and secure with a stopper. Shake by avoiding contact between the stopper and the liquid. Place the vial in a water bath at 60±1° for 2.0 hours.

Internal standard solution. Inject 10 µL of ethyl ether into 20.0 ml of *N,N-dimethylacetamide* by immersing the tip of the needle in the solvent using a microsyringe. Immediately before use, dilute the solution with *N,N-dimethylacetamide* to 1000 times its volume.

Vinyl chloride primary solution:

NOTE—Prepare under a ventilated hood.

Place 50.0 ml of *N,N-dimethylacetamide* in a 50-ml vial, stopper the vial, secure the stopper, and weigh to the nearest 0.1 mg. Fill a 50-ml polyethylene or polypropylene syringe with gaseous vinyl chloride, allow the gas to remain in contact with the syringe for about 3 minutes, empty the syringe, and fill again with 50.0 ml of gaseous vinyl chloride. Fit a hypodermic needle to the syringe, and reduce the volume of gas in the syringe from 50 to 25.0 ml. Inject the remaining 25.0 ml of vinyl chloride slowly into the vial, shaking gently and avoiding contact between the liquid and the needle. Weigh the vial again; the increase in mass is about 60 mg (1 µl of the solution obtained contains about 1.2 µg of vinyl chloride). Allow to stand for 2 hours. Store the primary solution in a refrigerator.

Vinyl chloride standard solution.

To one volume of the Vinyl chloride primary solution add three volumes of *N,N-dimethylacetamide.*

Reference solutions. Place 10.0 ml of the Internal standard solution in each of six 50.0 ml vials. Close the vials, and secure the stoppers. Inject 1, 2, 3, 5, and 10 µl, respectively, of the Vinyl chloride standard solution into five of the vials. The six solutions thus obtained contain, respectively, 0, 0.3, 0.6, 0.9, 1.5, and 3 µg of vinyl chloride. Shake, avoiding contact between the stopper and the liquid. Place the vials in a water bath at 60 ± 1° for 2 hours.

Chromatographic system

- a stainless steel column 3 m x 3.0 mm, packed with with silanized diatomaceous earth for gas chromatography impregnated with 5per cent m/m of dimethylstearylamide and 5per cent m/m of *polyethylene glycol 400*,
- temperature:
  column. 45°,
  inlet port. 100°,
  detector at 150°,
- flow rate: 30 ml per minute, using nitrogen as carrier gas,

Inject 1ml of the head space of each vial containing the test solution and the Reference solutions.

Calculate the amount of vinyl chloride in the test solution by comparing the test result of the Sample solution with the test results of the reference solutions. Calculate the amount of vinyl chloride in the test material by dividing the amount of vinyl chloride in the test solution by 1.0 g, producing a result in µg per g or ppm.

Not more than 1 ppm. Note that vinyl chloride is not an additive but is monitored as a residual monomer.

B.3.1. Chlorine

50.0 mg of the test material is processed using Oxygen Flask method (2.3.34). Absorb the combustion products with 20.0 ml of *1M sodium hydroxide*. To this, add 2.5 ml of *nitric acid*, 10.0 ml of *0.1 M silver nitrate* solution, 5.0 ml of *ferric ammonium sulphate solution*, and 1ml of *dibutyl phthalate*. Titrate with *0.005Mammonium thiocyanate* solution until a reddish-yellow colour is obtained. Carry out a blank titration.

Calculate the titration volume by subtracting the volume of titrant used in the blank from the volume of titrant used in the Preparation. Each ml of *0.005 M ammonium thiocyanate* is equal to 6.25 mg of polyvinyl chloride. The chlorine content, in weight per cent, is calculated as follows:

$$\text{Chlorine content (weight per cent)} = \frac{\text{Titrant volume (ml)} \times 6.25 \text{ mg per ml}}{\text{Weight of sample (mg)}} \times 100 \text{ per cent}$$

Not less than 80 per cent by weight, expressed as polyvinyl chloride.

B.4. Total organic carbon

The total organic content of Solution S1 is measured according to the general methodologies outlined in Total Organic Carbon (2.4.30).

The method used to perform the total organic carbonanalysis should have a limit of detection of 0.2 mg per litre (ppm) and should have a demonstrated linear dynamic range from 0.2 to 20 mg per litre (which encompasses the total organic carbon limit). A linear range with a higher upper concentration can be used if linearity is established. If sample extracts exceed this upper linear range, they must be diluted appropriately for analysis.

The difference between the sample and blank total organic carbon concentrations is not more than 5 mg per litre.

B.5. Extractable Metals

Solution S3 is used for acid extractable metals.

Procedure for extract analysis

Instrumentation and methods are those specified in Elemental Impurities (2.3.13A).

Aluminium, arsenic, lead, cadmium, mercury, cobalt, nickel, vanadium, and zinc. Report the measured value in Solution S3 at values above 0.01 mg per litre (ppm), corresponding to 0.025 µg per g. If the measured values are below these values, report the result as less than 0.01mg per litre (ppm), corresponding to less than 0.025 µg per g.

Additional acceptance criteria for materials used as containers for non-injectable aqueous solutions.

Barium. Solution S3 containsnot more than 0.10 mg per litre (ppm), corresponding to 2 µg per g.

Cadmium. Solution S3 contains not more than 0.03 mg per litre (ppm), corresponding to 0.6 µg per g.

Zinc. Solution S3 contains not more than 5 mg per litre (ppm), corresponding to 100 µg per g.

6.2.1.2.4.Polyvinyl Chloride (PVC, Plasticized) Containers

Polyvinyl Chloride is a polymer whose basic building blocks are Vinyl Chloride monomers. It is a Thermoplastic polymer.

Production of PVC

PVC is produced by Suspension Polymerisation or Emulsion Polymerisation or Bulk Polymerisation.

This virgin PVC is compounded with additives before conversion into finished products.

PVC can be plasticised using various plasticisers to make it flexible for use in medical products.

The resin and its conversion into containers may involve the use of colourants conforming to Indian Standards IS-9833 and/or additives conforming to IS-10148.

The manufacturers of containers should receive the certificate of analysis for each lot of resins procured from to confirm the quality of resins that the grade of resins used is as agreed and meets the relevant specification. The certificate of analysis from the resin manufacturer shall provide the necessary assurance about the quality of resin.

A. Identification of Container Material

Test 1 – By FTIR Spectrophotometry (2.4.6)

Determine the infrared spectrum from 3800 cm^{-1} to 600 cm^{-1}. The specimen exhibits an absorption spectrum that is substantially equivalent to that of the *polyvinyl chloride, plasticized RS*. Substantial, as opposed to exact, equivalence allows for minor spectral differences arising from the natural compositional and/or physical variation among polymers of this class. Substantial equivalence is achieved when all differences between the sample andreferencespectra can be explained in the context of such natural compositional and/or physical variations.

Test 2 – By Differential Scanning Calorimetry(2.4.31)

Conduct the entire test under nitrogen. Heat the specimen from -20° to 120° at a heating rate between 2° and 10° per minutes. For protecting the instrument, rapidly cool the specimento room temperature. This thermogram is to be used for comparison.

Compare the thermogram of the specimen with that of the reference PVC, Plasticized. The glass transition temperature obtained from the thermogram of the specimen does not differ from that of the reference thermogram by more than 8.0°.

NOTE—The results of the DSC analysis are strongly dependent on the amount of plasticizer in the test article.

B. Chemical Tests

Preparation of Special Solutions for subsequent tests on Polyvinyl Chloride

Solution S1 (Water extraction)

Place 25 g of the test material into a borosilicate glass flask. Add 500 ml of purified water, cover the flask's neck with aluminium foil or a borosilicate beaker, and heat in an autoclave at 121 ± 2° for 20 minutes. Allow the solution to cool and the solids to settle, decant the solution into a 500-ml volumetric flask, and dilute with purified water to volume; the diluted solution is *Solution S1*.

Solution S2 (Tetrahydrofuran extraction)

Dissolve 5.0 g of the test material in 80 ml of *tetrahydrofuran* and dilute to a volume of 100.0 ml with the same solvent. Filter

if necessary; the solution may remain opaque. Slowly and drop wise add 70 ml *ethanol* to 20.0 ml of this solution. Cool the mixture in ice for 1 hour. Filter or centrifuge the mixture, collecting residue A. Wash residue A with ethanol. Collect the washings and add them to the solution remaining after filtration or centrifugation. Transfer the solution to a 100.0 ml volumetric flask and dilute to volume with ethanol. This process produces *Solution S2*. Prepare a blank solution.

Solution S3 (Acid extraction)

Place 5 g in a borosilicate glass flask with a ground-glass neck. Add 100.0 ml of *0.1 M hydrochloric acid*, and boil under a reflux condenser for 1 hour with constant stirring. Allow to cool and the solids to settle, decant the solution into a 100.0 ml volumetric flask, and dilute to volume with *0.1 M hydrochloric acid*; the diluted solution is *Solution S3*.

Tests Using Special Solutions

B.1. Absorbance (2.4.7)

Evaporate 100.0 ml of Solution S1 to dryness. Dissolve the resulting residue in 5.0 ml of hexane to produce the hexane sample. Pass the hexane sample, if necessary, through a filter previously rinsed with hexane. Determine the spectrum between 250 and 310 nm in the hexane sample.

Absorbanceshould not bemore than 0.25.

B.2. Acidity or alkalinity

To 100.0 ml of Solution S1 add 0.15 ml of *BRP indicator solution*. Determine the titration volume of *0.01 M sodium hydroxide* required to change the colour of the indicator to blue. To 100.0 ml of Solution S1 add 0.2 ml of *Methyl orange solution*. Determine the titration volume of *0.01 M hydrochloric acid* required to reach the beginning of the colour change of the indicator from yellow to orange.

Not more than 1.5 ml of *0.01 N sodium hydroxide* is required to change the colour of the indicator to blue. Not more than 1.0 ml of *0.01 N hydrochloric acid* is required to reach the beginning of the colour change of the indicator from yellow to orange.

B.3. Polymer Additives

Determine by thin-layer chromatography (2.4.17), using the plate coated with silica gel *GF254 (1 mm thick)*.

Additives are di(2-ethylhexyl) phthalate, N,N_3-diacylethylenediamines, epoxidized soya oil, and epoxidized linseed oil. Vinyl chloride monomer (VCM) is also monitored, although it is a residual monomer and not an additive.

Mobile Phase. Toluene.

Solution A1. Add 2.0 g of the test material to 200.0 ml of peroxide-free ether and heat under a reflux condenser for 8 hours. Separate the resulting residue B and extraction solution A by filtration. Evaporate extraction solution A to dryness under reduced pressure in a water bath at 30°, producing residue C. Dissolve residue C in 10.0 ml of toluene.

Precipitate B2. Dissolve residue B in 60 ml of *ethylene chloride* heating on a water bath under a reflux condenser, producing solution D. Filter the resulting solution D. Add the filtered solution D drop wise and with vigorous shaking to 600 ml of heptanes heated almost to boiling. Separate by hot filtration the coagulum B1 and the organic solution E. Allow solution E to cool; separate the precipitate B2 that forms upon cooling, and pass through a tared sintered-glass filter (pore size of 16–40 µm).

Reference solution (u) 0.01 per cent of *polymer additive 14 RS* prepared in *toluene*.

Reference solution (v) 0.01 per cent of *polymer additive 15 RS* prepared in *toluene*.

Reference solution (w) 0.01 per cent of *polymer additive 16 RS* prepared in *toluene*.

Additive di(2-ethylhexyl) phthalate

Apply to the plate 0.5 ml of solution A to the plate as 30 mm x 30 mm. Apply 5 µl reference solution (u). Develop the plates over a path of 15 cm with toluene. After development, dry the plate in air and examine under UV light at 254 nm. Locate the zone corresponding to additive di(2-ethylhexyl) phthalate, *polymer additive 14 RS* (R_f about 0.4). Remove the area of silica gel corresponding to this zone, mix with 40 ml of *ethyl ether*, and shake for 1 minute. Filter, rinse filter with two quantities each of 10.0 ml of ethyl ether, add the rinsing to the filtrate, and evaporate to dryness. The residue weighs not more than 40 mg.

Residue is not more than 40 mg

Additives epoxidized soya oil and epoxidized linseed oil.

Apply to the plate 0.5 ml of solution A to the plate as 30 mm x 30 mm. Apply 5 µl reference solution (v) and reference solution (w). Develop the plates over a path of 15 cm with *toluene*. After development, dry the plate in air and expose to iodine vapor for 5 minutes. locate the zone corresponding to additive epoxidized soya oil, *polymer additive 15 RS* and epoxidized linseed oil, *polymer additive 16 RS* (R_f 0.0). Remove the area of silica gel corresponding to this band. Similarly, remove a corresponding area of silica gel as a blank reference. Separately mix both samples with separate 40 ml portions of *methanol*, shaking for 15 minutes. Filter, rinse the filter with two quantities of 10.0 ml of *methanol*, add the rinsing to the filtrate, and evaporate to dryness. The difference between the masses of both residues is not more than 10 mg.

Epoxidized soya oil. The difference between the masses of both residues is not more than 10 mg.

Epoxidized linseed oil. The difference between the masses of both residues is not more than 10 mg.

B.4. Total Organic Carbon

The total organic content of Solution S1 is measured according to the general methodologies outlined in Total Organic Carbon (2.4.30).

The method used to perform the Total Organic Carbonanalysis should have a limit of detection of 0.2 mg per litre (ppm) and should have a demonstrated linear dynamic range from 0.2 to 20 mg per litre (which encompasses the total organic carbon limit). A linear range with a higher upper concentration can be used if linearity is established. If sample extracts exceed this upper linear range, they must be diluted appropriately for analysis.

The difference between the sample and blank Total Organic Carbon concentrations is not more than 5 mg per litre.

B.5. Extractable Metals

Solution S3 is used for acid extractable metals.

Procedure for extract analysis

Instrumentation and methods are those specified in Elemental Impurities (2.3.13A).

Arsenic, cadmium, lead, mercury, cobalt, nickel, and vanadium. Report the measured value in *Solution S3* at values above 0.01 mg per litre (ppm), corresponding to 0.025 µg per g. If the measured values are below these values, report the result as less than 0.01 mg per litre (ppm), corresponding to less than 0.025 µg per g.

Barium. Solution S3 contains not more than 0.25 mg per litre (ppm), corresponding to 5 µg per g.

Calcium. Solution S3 contains not more than 35 mg per litre (ppm), corresponding to 0.07 weight per cent.

Tin. Solution S3 contains not more than 1 mg per litre (ppm), corresponding to 20 µg per g.

Zinc. Solution S3 contains not more than 100 mg per litre (ppm), corresponding to 0.2 weight per cent.

B.6. Related Substances (Residual Monomers/Residual Solvents)

B.6.1. Vinyl Chloride

*Internal standard solution.*Using a microsyringe, Inject 10 µL of *ethyl ether* into 20.0 ml of *N,N-dimethylacetamide*by immersing the tip of the needle in the solvent. Immediately before use, dilute 1.0 volume of the solution to 1000 volumes with *N,N-dimethylacetamide.*

Test solution. Place 1.0 g of the test material in a 50.0 ml vial, and add 10.0 ml of the internal standard solution. Close the vial, and secure with a stopper. Shake, avoiding contact between the stopper and the liquid. Place the vial in a water bath at 60 ± 1° for 2 hours.

Vinyl chloride primary solution:

NOTE—Prepare under a ventilated hood.

Place 50.0 ml of *N,N-dimethylacetamide* in a 50-ml vial, stopper the vial, secure the stopper, and weigh to the nearest 0.1 mg. Fill a 50-ml polyethylene or polypropylene syringe with gaseous vinyl chloride, allow the gas to remain in contact with the syringe for about 3 minutes, empty the syringe, and fill again with 50.0 ml of gaseous vinyl chloride. Fit a hypodermic needle to the syringe, and reduce the volume of gas in the syringe from 50 to 25.0 ml. Inject the remaining 25.0 ml of vinyl chloride slowly into the vial, shaking gently and avoiding contact between the liquid and the needle. Weigh the vial again; the increase in mass is about 60 mg (1 µl of the solution obtained contains about 1.2 µg of vinyl chloride). Allow to stand for 2 hours. Store the primary solution in a refrigerator.

Vinyl chloride standard solution. To one volume of the Vinyl chloride primary solution add three volumes of *N,N-dimethylacetamide.*

Reference solutions . Place 10.0 ml of the Internal standard solution in each of six 50.0 ml vials. Close the vials, and secure the stoppers. Inject 1, 2, 3, 5, and 10 µl, respectively, of the Vinyl chloride standard solution into five of the vials. The six solutions thus obtained contain, respectively, 0, 0.3, 0.6, 0.9, 1.5, and 3 µg of *vinyl chloride.* Shake, avoiding contact between the stopper and the liquid. Place the vials in a water bath at 60 ±1° for 2 hours.

Chromatographic system

- a stainless steel column 3.0 m x 3.0 mm, packed with silanized diatomaceous earth for gas chromatography impregnated with 5 per cent m/m of dimethylstearyl-amide and 5 per cent m/m of *polyethylene glycol 400*,
- temperature:
  column. 45°,
  inlet port. 100°,
  detector at 150°,
- flow rate: 30 ml per minute, using nitrogen as carrier gas.

Inject 1 ml of the head space of each vial containing the test solution and the reference solutions.

Calculate the amount of vinyl chloride in the test solution by comparing the test result of the Sample solution with the test results of the Reference solutions. Calculate the amount of vinyl chloride in the test material by dividing the amount of vinyl chloride in the test solution by 1.0 g, producing a result in µg per g or ppm.

Not more than 1ppm.

Note that vinyl chloride is not an additive but is monitored as a residual monomer.

6.2.1.2.5. .Polypropylene (PP) Containers

Polypropylene is manufactured by addition polymerisation of Propylene (C_3H_6), a gaseous hydrocarbon. PP is classified as thermoplastic polymer.

Production of Polypropylene

Production of polypropylene takes place where propylene monomer is subjected to heat and pressure in the presence of a catalyst system (preferably Zeiglar Natta Catalyst). Polymerisation is achieved at relatively low temperature of around 70° and pressures of around 30 bar and the product yielded is translucent.

The resin and its conversion into containers may involve the use of colourants conforming to Indian Standards IS-9833 and/or additives conforming to IS-10909.

The manufacturers of containers should receive the certificate of analysis for each lot of resins procured from to confirm the quality of resins that the grade of resins used is as agreed and meets the relevant specification. The certificate of analysis from the resin manufacturer shall provide the necessary assurance about the quality of resin.

A. Identification of Container Material

Test 1 – By FTIR Spectrophotometry (2.4.6)

Determine the infrared spectrum from 3800 cm^{-1} to 650 cm^{-1}. The specimen exhibits an absorption spectrum that is substantially equivalent to that of the homopolymer *polypropylene RS*. Substantial, as opposed to exact, equivalence allows for minor spectral differences arising from the natural compositional and/or physical variation among polymers of this class. Substantial equivalence is achieved when all differences between the sample andreferencespectra can be explained in the context of such natural compositional and/or physical variations.

Test 2 – By Differential Scanning Calorimetry (2.4.31)

Conduct the entire test under nitrogen. Heat the specimen from room temperatureto 30° above melting peak temperature (T_1) at a heating rate between 2° and 10° /minand hold it for 10 minutes. Cool the specimen at the same rateto 50° below the peak crystallization temperature and hold it for 1 minute. Reheat it to T_1 at the same rate. This reheats thermogram to be used for comparison.

Compare the thermogram of the specimen with that of the reference PP. The melting peak temperature obtained from the thermogram of the specimen does not differ from that of the reference thermogram by more than 12.0°.

B. Chemical Tests

Preparation of Special Solutions for subsequent tests on Polypropylene

Solution S1 (Water extraction)

Place 25 g of the test material in a borosilicate glass flask with a ground-glass neck. Add 500 ml of purified water, and boil under reflux conditions for 5 hours. Allow to cool to ambient temperature, and filter the extracting solution through a sintered-glass filter. Collect the filtrate in a 500 ml volumetric flask and dilute with purified water to volume; the diluted solution is *Solution S1*.

NOTE—Use Solution S1 within 4 hours of preparation.

Solution S2 (Toluene extraction)

Place 2.0 g of the test material in a 250-ml borosilicate glass flask with a ground-glass neck. Add 80 ml of toluene and boil under a reflux condenser for 1.5 hours, stirring constantly. Allow to cool to 60° and add 120.0 ml of methanol with continued stirring. Pass the resulting solution through a sintered-glass filter. Rinse the flask and the filter with 25.0 ml of a mixture of 40 volumes of toluene and 60 volumes of methanol add the rinsing to the filtrate, and dilute to 250 ml with the same mixture of solvents to produce *Solution S2*. Prepare a blank solution.

Solution S3 (Acid extraction)

Place 5 g in a borosilicate glass flask with a ground-glass neck. Add 100 ml of *0.1 M hydrochloric acid*, and boil under a reflux condenser for 1 hours with constant stirring. Allow to cool and the solids to settle, decant the solution into a 100.0 ml volumetric flask, and dilute to volume with *0.1 M hydrochloric acid*; the diluted solution is *Solution S3*

Tests Using Special Solutions

B.1. Absorbance (2.4.7)

Determine the spectrum between 220 and 340 nm in Solution S1.

Absorbanceshould be not more than 0.2.

B.2. Acidity or alkalinity

To 100.0 ml of Solution S1 add 0.15 ml of BRP indicator solution. Determine the titration volume of *0.01 M sodium hydroxide* required to change the colour of the indicator to blue. To a separate, 100.0 ml portion of Solution S, add 0.2ml of *Methyl orange solution*. Determine the titration volume of *0.01 M hydrochloric acid* required to reach the beginning of the colour change of the indicator from yellow to orange.

Not more than 1.5 ml of *0.01 N sodium hydroxide* is required to change the colour of the indicator to blue.

Not more than 1.0 ml of *0.01 N hydrochloric acid* is required to reach the beginning of the colour change of the indicator from yellow to orange.

B.3. Polymer Additives

These tests should be carried out in whole or in part as required due to the stated composition of the material.

B.3.1. Phenolic Antioxidant

Solvent mixture. Mixture of equal volumes of *acetonitrile* and *tetrahydrofuran*.

Sample solution S2A. Evaporate 50 ml of Solution S2 to dryness under vacuum at 45°. Dissolve the resulting residue with 5.0 ml of the Solvent mixture. Prepare a blank solution from the blank solution corresponding to Solution S2.

Sample solution S2B. Evaporate 50 ml of Solution S2 to dryness under vacuum at 45°. Dissolve the residue with 5.0 ml of *methylene chloride.* Prepare a blank solution from the blank solution corresponding to Solution S2.

Reference solutions of the following reference solutions, prepare only those that are necessary for the analysis of the phenolic antioxidants stated in the composition of the substance to be examined.

Reference solution (a). A 0.01 per cent w/v of *butylated hydroxytoluene RS* and 0.024 per cent w/v of *polymer additive 01 RS* in the solvent mixture.

Reference solution (b). A 0.024per cent w/v of *polymer additive 02 RS* and 0.024 per cent of *polymer additive 03 RS* in the solvent mixture.

Reference solution *(c).* A 0.024 per cent of *polymer additive 04 RS* and 0.024per cent of *polymer additive 05 RS* in *methylene chloride.*

Reference solution (d). A 0.01 per cent of *butylated hydroxytoluene RS* in the solvent mixture.

Reference solution (e). A 0.024 per cent of *polymer additive 01 RS* in the solvent mixture.

Reference solution (f). A 0.024 per cent of *polymer aditive 06 RS* prepared in the solvent mixture.

Reference solution (g). A 0.024 per cent of *polymer additive 02 RS* prepared in the solvent mixture

Reference solution (h). A 0.024 per cent of *polymer additive 03 RS* prepared in the solvent mixture.

Reference solution (i). A 0.024 per cent of *polymer additive 04 RS* prepared in *methylene chloride.*

Reference solution (j). A 0.024 per cent of *polymer additive 05 RS* prepared in *methylene chloride.*

Test A

Determine by liquid chromatography (2.4.14).

If the substance to be examined contains additive butylated hydroxytoluene and/or additive ethylene bis[3,3-bis[3-(1,1dimethylethyl)-4-hydroxyphenyl]butanoate.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica microparticles (5 µm),
- mobile phase: a mixture of 70 volumes of a *acetronitrile* and 30 volumes of *water,*
- flow rate: 2.0 ml per minute,
- spectrophotometer set at 280 nm,
- injection volume: 20 µl.

Inject reference solution (a).The test is not valid unless the resolution between the peaks due to additive butylated-hydroxytolueneand additive ethylene bis[3,3-bis[3-(1,1-dimethylethyl)-4-hydroxyphenyl]butanoate] peaks is not less than 8.0.

Inject Sample solution S2A, corresponding blank solution, and Reference solution (d), Reference solution (e), or both. Run the chromatogram for about 30 minutes. The peak areas of Sample solution S2A are less than the corresponding peak areas of Reference solution (d) or Reference solution (e).

NOTE—Sample solution S2A shows only peaks caused by antioxidants stated in the composition and minor peaks that also correspond to the blank solution.

Test B

If the substance to be examined contains one or more of the following antioxidants pentaerythrityl tetrakis[3-(3,5-di tert-butyl-4-hydroxyphenyl)propionate; 2,2,23 ,6,6,63 -hexa-tert-butyl-4,4,43 -[(2,4,6-trimethyl-1,3,5-benzene-triyl)trism-ethylene]triphenol; octadecyl 3-(3,5-di-tert-butyl-4-hydroxy-phenyl)propionate; tris(2,4-di-tert-butylphenyl) phosphate; 1,3,5-tris(3,5-di-tert-butyl-4-hydroxybenzyl)-s-triazine-2,4,6(1*H*,3*H*,5*H*)-trione

Determine by liquid chromatography (2.4.14).

Carry out the test as described in Test A with the following modifications

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica microparticles (5 µm),
- mobile phase: a mixture of 60 volumes of *acetronitrile,* 30 volumes of *tetrahydrofuran* and 10 volumes of *water,*
- flow rate: 1.5 ml per minute,
- spectrophotometer set at 280 nm,
- injection volume: 20 µl.

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to additive pentaerythrityl-tetrakis[3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate and additive 2,2',23 ,6,6',63 -hexa-tert-butyl-4,4',43 -[(2,4,6-trimethyl-1,3,5-benzene-triyl)trismethylene]triphenol is not less than 2.0.

Inject Sample solution S2A, corresponding blank solution, and any Reference solutions of the antioxidants listed above that are stated in the composition. The peak areas of Sample solution S2A are less than the corresponding peak areas of Reference solutions of the antioxidants that are listed above and that are stated in the composition.

NOTE—Sample solution S2A shows only peaks caused by antioxidants stated in the composition and minor peaks that also correspond to the blank solution.

Test C

If the substance to be examined contains additive octadecyl-3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate and/or additive tris(2,4-di-tert-butylphenyl) phosphite

Determine by liquid chromatography (2.4.14).

Chromatographic system

Carry out the test as described in Test A with the following modifications

- mobile phase: a mixture of 50 volumes of *methanol*, 40 volumes of *2 propanol* and 5.0 volumes of *water*,
- flow rate: 1.5 ml per minute.

Inject reference solution (c).The test is not valid unless the resolution between the peaks due to additive octadecyl-3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate and additive tris(2,4-di-tert-butylphenyl) phosphite peaks is not less than 2.0.

Inject Sample solution S2B, corresponding blank solution, and either Reference solutions (i) or Reference solution (j) of the antioxidants listed above that are stated in the composition. The peak areas of Sample solution S2B are less than the corresponding peak areas of Reference solutions of the antioxidants that are listed above and that are stated in the composition.

NOTE—Sample solution S2B shows only peaks caused by antioxidants stated in the composition and minor peaks that also correspond to the blank solution.

B.3.2. Non-Phenolic Antioxidant

Determine by thin-layer chromatography (2.4.17), using the plate coated with silica gel *GF254*.

Mobile phase A.Hexane

Mobile phase B. Methylene chloride

Methylene chloride, acidified. To 100.0 ml of methylene chloride, add 10.0 ml of *hydrochloric acid*, shake, allow to stand, and separate the two layers. Use the lower layer.

Sample solution S2C. Evaporate 100.0 ml of Solution S2 to dryness under vacuum at 45°. Dissolve the resulting residue with 2 ml of *methylene chloride* acidified.

Reference solution (m). A 0.6 per centw/v of *polymer additive 08 RS* in *methylene chloride*. Dilute 2 ml of the solution with *methylene chloride*, acidified to 10.0 ml.

Reference solution (n). A 0.6 per cent w/v of *polymer additive 09 RS* in *methylene chloride*. Dilute 2 ml of the solution with *methylene chloride*, acidified to 10.0 ml.

Reference solution (o). A 0.6 per cent w/v of *polymer additive 10 RS* in *methylene chloride*. Dilute 2 ml of the solution with *methylene chloride*, acidified to 10.0 ml.

Reference solution (p). A 0.6 per cent of *polymer additive 10 RS*, and 0.6 per cent of *polymer additive 09 RS* in *methylene chloride*. Dilute 2 ml of the solution with *methylene chloride*, acidified to 10.0 ml.

Apply to the plate 20 µl of sample solution S2C, reference solution (p) and the reference solutionscorresponding to all the phenolic and non-phenolic antioxidants expected to be present. Develop the plates over a path of 18 cm with Mobile phase A,dry in air, again develop the plate over a path of 17 cm with Mobile phase B and dry in air. Spray with alcoholic iodine solution, allow to stand for 10 to 15 minutes and examine under ultraviolet light at 254 nm. The test is not valid unless the chromatogram obtained with reference solution (p) shows two separate spot. Any spot in the chromatogram obtained with sample solution S2C is not more intense than the spot in the same position in the chromatogram of the corresponding reference solution.

B.3.3. Amides and Stearates

Use sample solution as sample solution S2C as described in Non-phenolic Antioxidants.

Reference solution (r). A 0.2 per cent of Stearic *Acid RS* prepared in *methylene chloride*.

Reference solution (s). A 0.2 per cent of *polymer additive 12 RS* prepared in *methylene chloride*.

Reference solution (t) A 0.2 per cent of *polymer additive 13 RS* prepared in *methylene chloride*.

Test A

Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254*.

Mobile phase. a mixture of 75 volume of *trimethylpantane* and 25 volumes of *alcohol*.

Apply to the plate 10 µl of sample solution S2C and reference solution (r). Develop the plate over a path of 10 cm with Mobile phase. After development, dry the plate in air, spray with 2 per cent 2,6-dichlorophenol-indophenol sodium in dehydrated alcohol, heat in an oven at 120° for a few minutes to intensify the spots and examineany spot corresponding to additive stearic acid in the chromatogram obtained with sample solution S2C (R_f = about 0.5) is not more intense than the spot in the same position in the chromatogram of reference solution (r).

Test B

Determine by thin-layer chromatography(2.4.17), using the plate coated with *silica gel GF254*.

Mobile phase A. Hexane.

Mobile phase B. A mixture of 95 volumes of *methylene chloride* and 5.0 volumes of *methanol*.

Apply to the plate 10 µl of sample solution S2C, reference solution (s) and reference solution (t). Develop the plates over a path of 13 cm with Mobile phase A andover a path of 10 cm with Mobile phase B respectively. After each development,

dry the plate in air, spray with 40 per cent *phosphomolybdic acid* in *alcohol* heat in an oven at 120° for a few minutes to intensify the spots and examineany spot corresponding to additive oleamide or erucamide in the chromatogram obtained with sample solution S2C (R_f= about 0.2) is not more intense than the spot in the same position in the chromatogram of reference solution (s) and reference solution (t).

B.4. Total organic carbon

The total organic content of Solution S1 is measured according to the general methodologies outlined in Total Organic Carbon (2.4.30).

The method used to perform the Total Organic Carbon analyses should have a limit of detection of 0.2 mg per litre (ppm) and should have a demonstrated linear dynamic range from 0.2 to 20 mg per litre (which encompasses the total organic carbon limit). A linear range with a higher upper concentration can be used if linearity is established. If sample extracts exceed this upper linear range, they must be diluted appropriately for analysis.

The difference between the sample and blank Total Organic Carbon concentrations is not more than 5 mg per litre.

B.5. Extractable Metals

Solution S3 is used for acid extractable metals.

Procedure for extract analysis

Instrumentation and methods are those specified in Elemental Impurities (2.3.13A)

Aluminium. *Solution S3* contains not more than 0.4 mg per litre (ppm), corresponding to 1 µg per g.

Arsenic, cadmium, lead, mercury, cobalt, nickel, and vanadium. Report the measured value in Solution S3 at values above 0.01 mg per litre (ppm), corresponding to 0.025 µg per g. If the measured values are below these values, report the result as less than 0.01 mg per litre (ppm), corresponding to less than 0.025 µg per g.

Chromium. *Solution S3* contains not more than 0.02 mg per litre (ppm), corresponding to 0.05 µg per g.

Titanium. *Solution S3* contains not more than 0.4 mg per litre (ppm), corresponding to 1 µg per g.

Zinc. *Solution S3* contains not more than 0.4 mg per litre (ppm), corresponding to 1 µg per g.

6.2.1.2.6. Containers based on Cyclic Olefins

A. Identification of Container Material

Test 1 – By FTIR Spectrophotometry (2.4.6)

Determine the infrared spectrum from 3800 cm^{-1} to 650 cm^{-1}. The specimen exhibits an absorption spectrum that is substantially equivalent to that of *cyclic olefin polymer RS* or *cyclic olefin copolymer RS*. Substantial, as opposed to exact, equivalence allows for minor spectral differences arising from the natural compositional and/or physical variation among polymers of this class. Substantial equivalence is achieved when all differences between the sample andreferencespectra can be explained in the context of such natural compositional and/or physical variations.

Test 2 – By Differential Scanning Calorimetry (2.4.31)

Given the amorphous nature of these polymers and their compositional variety, material-to-material variations in the melting peak temperature can be anticipated. Thus, it is neither recommended nor required that differential scanning calorimetry (DSC) be performed.

B. Chemical Tests

Preparation of Special Solutions for subsequent tests on Cyclic Olefins

Solution S1 (Water extraction)

Place 25 g of the test material in a borosilicate glass flask with a ground-glass neck. Add 500 ml of purified water, and boil under reflux conditions for 5 hours. Allow to cool to ambient temperature, and filter the extracting solution through a sintered-glass filter. Collect the filtrate in a 500 ml volumetric flask and dilute with purified water to volume; the diluted solution is *Solution S1*.

NOTE—Use Solution S1 within 4 hours of preparation.

Solution S2 (Toluene extraction)

Place 2.0 g of the test material in a 250-ml borosilicate glass flask with a ground-glass neck. Add 80 ml of toluene and boil under a reflux condenser for 1.5 hours, stirring constantly. Allow to cool to 60° and add 120.0 ml of methanol with continued stirring. Pass the resulting solution through a sintered-glass filter. Rinse the flask and the filter with 25.0 ml of a mixture of 40 volumes of toluene and 60 volumes of methanol add the rinsing to the filtrate, and dilute to 250 ml with the same mixture of solvents to produce *Solution S2*. Prepare a blank solution.

Solution S3 (Acid extraction)

Place 5 g in a borosilicate glass flask with a ground-glass neck. Add 100.0 ml of *0.1 M hydrochloric acid*, and boil under a reflux condenser for 1 hour with constant stirring. Allow to cool and the solids to settle, decant the solution into a 100.0ml volumetric flask, and dilute to volume with *0.1 M hydrochloric acid*; the diluted solution is *Solution S3*.

Tests Using Special Solutions

B.1. Absorbance (2.4.7)

Determine the spectrum between 220 and 340 nm in Solution S1. Absorbanceshould be not more than 0.2.

B.2. Acidity or alkalinity

To 100.0 ml of Solution S1 add 0.15 ml of BRP indicator solution. Determine the titration volume of *0.01 M sodium hydroxide* required to change the colour of the indicator to blue. To a separate, 100.0 ml portion of Solution S, add 0.2 ml of *Methyl orange solution*. Determine the titration volume of *0.01 M hydrochloric acid* required to reach the beginning of the colour change of the indicator from yellow to orange.

Not more than 1.5 ml of *0.01 N* sodium hydroxide is required to change the colour of the indicator to blue. Not more than 1.0 ml of *0.01 N hydrochloric acid* is required to reach the beginning of the colour change of the indicator from yellow to orange.

B.3. Polymer Additives

These tests should be carried out in whole or in part as required due to the stated composition of the material.

B.3.1. Phenolic Antioxidant

Solvent mixture. a mixture of equal volumes of *acetonitrile* and *tetrahydrofuran*.

Sample solution S2A. Evaporate 50.0 ml of Solution S2 to dryness under vacuum at 45°. Dissolve the resulting residue with 5.0ml of the Solvent mixture. Prepare a blank solution from the blank solution corresponding to Solution S2.

Sample solution S2B. Evaporate 50.0 ml of Solution S2 to dryness under vacuum at 45°. Dissolve the residue with 5.0 ml of methylene chloride. Prepare a blank solution from the blank solution corresponding to Solution S2.

Of the following reference solutions; prepare only those that are necessary for the analysis of the phenolic antioxidants stated in the composition of the substance to be examined.

Reference solution (a). A 0.01 per cent w/v of *butylated hydroxytoluene RS* and 0.024 per cent w/v of *polymer additive 01 RS* in the Solvent mixture.

Reference solution (b). A 0.024 per cent w/v of *polymer additive 02 RS* and 0.024 per cent of *polymer additive 03 RS* in the Solvent mixture.

Reference solution *(c)*. A 0.024 per cent of *polymer additive 04 RS* and 0.024 per cent of *polymer additive 05 RS* in *methylene chloride.*

Reference solution (d). A 0.01 per cent of *butylated hydroxytoluene RS* in the solvent mixture.

Reference solution (e). A 0.024 per cent of *polymer additive 01 RS* in the solvent mixture.

Reference solution (f). A 0.024 per cent of *polymer additive 06 RS* prepared in the solvent mixture.

Reference solution (g). A 0.024 per cent of *polymer additive 02 RS* prepared in the solvent mixture.

Reference solution (h). A 0.024 per cent of *polymer additive 03 RS* prepared in the solvent mixture.

Reference solution (i). A 0.024 per cent of *polymer additive 04 RS* prepared in *methylene chloride.*

Reference solution (j). A 0.024 per cent of *polymer additive 05 RS* prepared in *methylene chloride*

Test A

Determine by liquid chromatography (2.4.14).

If the substance to be examined contains additive butylatedhydroxytoluene and/or additive ethylene bis[3,3-bis[3-(1,1dimethylethyl)-4-hydroxyphenyl]butanoate

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica microparticles (5µm),
- mobile phase: a mixture of 70 volumes of *acetronitrile* and 30 volumes of *water*,
- flow rate: 2 ml per minute,
- spectrophotometer set at 280 nm,
- injection volume: 20 µl.

Inject reference solution (a).The test is not valid unless the resolution between the peaks due to additive butylatedhydroxytolueneand additive ethylene bis[3,3-bis[3-(1,1-dimethylethyl)-4-hydroxyphenyl]butanoate] peaks is not less than 8.0.

Inject Sample solution S2A, corresponding blank solution, and Reference solution (d), Reference solution (e), or both. Run the chromatogram for about 30 minutes. The peak areas of Sample solution S2A are less than the corresponding peak areas of Reference solution (d) or Reference solution (e).

NOTE—Sample solution S2A shows only peaks caused by antioxidants stated in the composition and minor peaks that also correspond to the blank solution.

Test B

If the substance to be examined contains one or more of the following antioxidants pentaerythrityltetrakis[3-(3,5-di tert-butyl-4-hydroxyphenyl)propionate; 2,2,23 ,6,6,63 -hexa-tert-butyl-4,4,43 -[(2,4,6-trimethyl-1,3,5-benzene-triyl) tris-methylene]triphenol; octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate; tris(2,4-di-tert-butylphenyl) phosphite; 1,3,5-tris(3,5-di-tert-butyl-4-hydroxybenzyl)-s-triazine-2,4,6(1*H*,3*H*,5*H*)-trione

Chromatographic system Determine by liquid chromatography (2.4.14). Carry out the test as described in Test A with the following modifications

- mobile phase: a mixture of 60 volumes of *acetronitrile* 30 volumes of *tetrahydrofuran* and 10 volumes of *water*,
- flow rate: 1.5 ml per minute.

Inject reference solution (b).The test is not valid unless the resolution between the peaks due to additive pentaerythrityl-tetrakis[3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate and additive 2,2',23 ,6,6',63 -hexa-tert-butyl-4,4',43 -[(2,4,6-

trimethyl-1,3,5-benzene-triyl)trismethylene]triphenol peaks is not less than 2.0.

Inject Sample solution S2A, corresponding blank solution,and any Reference solutions of the antioxidants listed above that are stated in the composition. The peak areas of Sample solution S2A are less than the corresponding peak areas of Reference solutions of the antioxidants that are listed above and that are stated in the composition.

NOTE—Sample solution S2A shows only peaks caused by antioxidants stated in the composition and minor peaks that also correspond to the blank solution.

Test C

If the substance to be examined contains additive octadecyl-3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate and/or additive tris(2,4-di-tert-butylphenyl) phosphite.

Chromatographic system Determine by liquid chromatography (2.4.14). Carry out the test as described in Test A with the following modifications

- mobile phase: a mixture of 50 volumes of *methanol*, 40 volumes of *2 propanol* and 5.0 volumes of *water,*
- flow rate: 1.5 ml per minute.

Inject reference solution (c). The test is not valid unless the resolution between the peaks due to additive octadecyl-3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate and additive tris(2,4-di-tert-butylphenyl) phosphite peaks is not less than 2.0.

Inject Sample solution S2B, corresponding blank solution, and either Reference solutions (i) or Reference solution (j) of the antioxidants listed above that are stated in the composition. The peak areas of Sample solution S2B are less than the corresponding peak areas of Reference solutions of the antioxidants that are listed above and that are stated in the composition.

NOTE—Sample solution S2B shows only peaks caused by antioxidants stated in the composition and minor peaks that also correspond to the blank solution.

B.3.2. Non-phenolic Antioxidant

Determine by thin-layer chromatography(2.4.17), using the plate coated with silica *gel GF254.*

Mobile phase A. Hexane.

Mobile phase B. Methylene chloride.

Methylene chloride, acidified. To 100.0 ml of *methylene chloride* add 10.0 ml of *hydrochloric acid*, shake, allow to stand, and separate the two layers. Use the lower layer.

Sample solution S2C. Evaporate 100.0 ml of Solution S2 to dryness under vacuum at 45°. Dissolve the resulting residue with 2 ml of *methylene chloride* acidified.

Reference solution (m). 0.6 per cent w/v of *polymer additive 08 RS* in *methylene chloride*. Dilute 2 ml of the solution with *methylene chloride*, acidified to 10 ml.

Reference solution (n). 0.6 per cent w/v of *polymer additive 09 RS* in *methylene chloride*. Dilute 2 ml of the solution with *methylene chloride*, acidified to 10 ml.

Reference solution (o). 0.6 per cent w/v of *polymer additive 10 RS* in *methylene chloride*. Dilute 2 ml of the solution with *methylene chloride*, acidified to 10 ml.

Reference solution (p). 0.6 per cent of *polymer additive 10 RS*, and 0.6 per cent of *polymer additive 09 RS* in *methylene chloride*. Dilute 2 ml of the solution with *methylene chloride*, acidified to 10 ml.

Apply to the plate 20 µl of sample solution S2C, reference solution (p) and the reference solutions corresponding to all the phenolic and non-phenolic antioxidants expected to be present. Develop the plates over a path of 18 cm with Mobile phase A anddry in air, again develop the plate over a path of 17 cm with Mobile phase B and dry in air. Spray with alcoholic iodine solution, allow to stand for 10 to 15 minutes and examine under ultraviolet light at 254 nm.

The test is not valid unless the chromatogram obtained with reference solution (p) shows two separate spot. Any spot in the chromatogram obtained with sample solution S2C is not more intense than the spot in the same position in the chromatogram of the corresponding reference solution.

B.3.3. Copolymer of Dimethyl Succinate and (4-Hydroxy-2,2,6,6-tetramethylpiperidin-1-yl) ethanol

Determine by liquid chromatography (2.4.14).

Solvent mixture. 89 volume of *hexane* and 11 volumes of *methanol.*

Sample solution S2D. Evaporate 25 ml of Solution S2 to dryness under vacuum at 45°. Dissolve the residue with 10 ml of *toluene* and 10 ml of a 10 per cent w/v solution of *tetrabutyl ammonium hydroxide* in a mixture of 35 volumes of *toluene* and 65 volumes of *anhydrous methanol*. Boil under a reflux condenser for 3 hours. Allow to cool, and filter.

Reference solution (q). A 0.06 per cent w/v of *polymer additive 11 RS* prepared in *toluene*. Add 1.0 ml of this solution to 25 ml of the blank solution corresponding to Solution S2 and evaporate to dryness under vacuum at 45°. Prepare a blank solution from the blank solution corresponding to solution S2. Dissolve the residue with 10 ml of toluene and 10 ml of a 10 per cent w/v solution of *tetrabutyl ammonium hydroxide* in a mixture of 35 volumes of *toluene* and 65 volumes of *anhydrous methanol*. Boil under a reflux condenser for 3 hours. Allow to cool, and filter.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with aminopropylsilane bonded to porous silica microparticles (5 µm),
- mobile phase: a mixture of 89 volume of *hexane* and 11 volumes of *methanol*,
- flow rate: 2 ml per minute,

- spectrophotometer set at 227 nm,
- injection volume: 20 µl.

Inject reference solution (q). The test is not valid unless the resolution between the peaks due to diol component and the diluents peaks is not less than 7.0.

Inject Sample solution S2D corresponding blank solution and Reference solution (q). Run the chromatogram for about 30 minutes. The peak areas of diol component in Sample solution S2A are less than the corresponding peak areas of teference solution (q).

B.3.4. Amides and Stearates

Use sample solution as sample solution S2C as described in Non-phenolic Antioxidants.

Reference solution (r). A 0.2 per cent of *stearic acid RS* prepared in *methylene chloride.*

Reference solution (s). A 0.2 per cent of *polymer additive 12 RS* prepared in *methylene chloride.*

Reference solution (t). A 0.2 per cent of *polymer additive 13 RS* prepared in *methylene chloride.*

Test A

Determine by thin-layer chromatography (2.4.17), coating the plate with *silica gel GF254.*

Mobile phase. a mixture of 75 volume of *trimethylpentane* and 25 volumes of *alcohol.*

Apply to the plate 10 µl of sample solution S2C and reference solution (r). Develop the plate over a path of 10 cm with Mobile phase. After development, dry the plate in air, spray with 2 per cent 2,6-dichlorophenol-indophenol sodium in dehydrated alcohol, heat in an oven at 120° for a few minutes to intensify the spots and examineany spot corresponding to additive stearic acid in the chromatogram obtained with sample solution S2C (R_f= about 0.5) is not more intense than the spot in the same position in the chromatogram of reference solution (r).

Test B

Determine by thin-layer chromatography (2.4.17), using the plate coated with silica *gel GF254.*

Mobile phase A. Hexane.

Mobile phase B. A mixture of 95 volumes of *methylene chloride* and 5.0 volumes of *methanol.*

Apply to the plate 10 µl of sample solution S2C, reference solution (s) and reference solution (t). Develop the plates over a path of 13 cm with Mobile phase A andover a path of 10 cm with Mobile phase B respectively. After each development, dry the plate in air, spray with 40 per cent *phosphomolybdic acid* in *alcohol,* heat in an oven at 120° for a few minutes to intensify the spots and examine any spot corresponding to additive oleamide or erucamide in the chromatogram obtained with sample solution S2C (R_f= about 0.2) is not more intense than the spot in the same position in the chromatogram of reference solution (s) and reference solution (t).

B.4. Total Organic Carbon

The total organic content of Solution S1 is measured according to the general methodologies outlined in Total Organic Carbon (2.4.30).

The method used to perform the Total Organic Carbon analyses should have a limit of detection of 0.2 mg per litre (ppm) and should have a demonstrated linear dynamic range from 0.2 to 20 mg per litre (which encompasses the TOC limit). A linear range with a higher upper concentration can be used if linearity is established. If sample extracts exceed this upper linear range, they must be diluted appropriately for analysis.

The difference between the sample and blank total organic carbon concentrations is not more than 5 mg/L.

B.5. Extractable Metals

Solution S3 is used for acid extractable metals.

Procedure for extract analysis

Instrumentation and methods are those specified in Elemental Impurities (2.3.13A)

Aluminium. Solution S3 contains not more than 0.4 mg per litre (ppm), corresponding to 1 µg per g.

Arsenic, cadmium, lead, mercury, cobalt, nickel, and vanadium. Report the measured value in Solution S3 at values above 0.01 mg per litre (ppm), corresponding to 0.025 µg per g. If the measured values are below these values, report the result as less than 0.01 mg per litre (ppm), corresponding to less than 0.025 µg per g.

Titanium. Solution S3 contains not more than 0.4 mg per litre (ppm), corresponding to 1 µg per g.

Zinc. Solution S3 contains not more than 0.4 mg per litre (ppm), corresponding to 1 µg per g.

6.2.1.2.7.Poly(Ethylene-vinyl Acetate) (PEVA) Containers

A. Identification of Container Material

Test 1 – By FTIR Spectrophotometry (2.4.6)

Determine the infrared spectrum from 4400 cm^{-1} to 650 cm^{-1}. The specimen exhibits an absorption spectrum that is substantially equivalent to that of *poly(ethylene-vinyl acetate) RS.* Substantial, as opposed to exact, equivalence allows for minor spectral differences arising from the natural compositional and/or physical variation among polymers of this class. Substantial equivalence is achieved when all differences between the sample andreferencespectra can be explained in the context of such natural compositional and/or physical variations.

Test 2 – By Differential Scanning Calorimetry (2.4.31)

Conduct the entire test under nitrogen. Heat the specimen from "50° to 120° at a heating rate between 2° and 10° /minute. For protecting the instrument,rapidly cool the specimento 40° at the same rate.

Compare the thermogram of the specimen with that of the reference PEVA. The transition temperature obtained from the thermogram of the specimen does not differ from that of the reference thermogram by more than 6.0°.

B. Chemical Tests

Preparation of Special Solutions for subsequent tests on Poly(ethylene-vinyl acetate)

Solution S1 (Water extraction)

Place 25 g of the test material in a borosilicate glass flask with a ground-glass neck. Add 500 ml of purified water, and boil under reflux conditions for 5 hours. Allow to cool to ambient temperature, and filter the extracting solution through a sintered-glass filter. Collect the filtrate in a 500 ml volumetric flask and dilute with purified water to volume; the diluted solution is *Solution S1*.

NOTE—Use Solution S1 within 4 hours of preparation.

Solution S2 (Toluene extraction)

Place 2.0 g of the test material in a 250-ml borosilicate glass flask with a ground-glass neck. Add 80 ml of toluene and boil under a reflux condenser for 1.5 hours, stirring constantly. Allow to cool to 60° and add 120.0 ml of *methanol* with continued stirring. Pass the resulting solution through a sintered-glass filter. Rinse the flask and the filter with 25.0 ml of a mixture of 40 volumes of toluene and 60 volumes of methanol add the rinsing to the filtrate, and dilute to 250 ml with the same mixture of solvents to produce *Solution S2*. Prepare a blank solution.

Solution S3 (Acid extraction)

Place 5g in a borosilicate glass flask with a ground-glass neck. Add 100.0 ml of *0.1 M hydrochloric acid*, and boil under a reflux condenser for 1 hours with constant stirring. Allow to cool and the solids to settle, decant the solution into a 100.0 ml volumetric flask, and dilute to volume with *0.1 M hydrochloric acid*; the diluted solution is *Solution S3*.

Tests Using Special Solutions

B.1. Absorbance (2.4.7)

Determine the spectrum between 220 and 340 nm in Solution S1.

Absorbance should be not more than 0.2.

B.2. Acidity or alkalinity

To 100.0 ml of Solution S1 add 0.15 ml of *BRP indicator solution*. Determine the titration volume of *0.01 M sodium hydroxide* required to change the colour of the indicator to blue. To a separate, 100.0 ml portion of Solution S, add 0.2 ml of *Methyl orange solution*. Determine the titration volume of *0.01 M hydrochloric acid* required to reach the beginning of the colour change of the indicator from yellow to orange.

Not more than 1.0 ml of *0.01 N hydrochloric acid* is required to reach the beginning of the colour change of the indicator from yellow to orange.

B.3. Polymer Additives

These tests should be carried out in whole or in part as required due to the stated composition of the material.

B.3.1. Phenolic Antioxidants

Solvent mixture. A mixture of equal volumes of *acetonitrile* and *tetrahydrofuran.*

Sample solution S2E. Evaporate 50.0 ml of Solution S2 to dryness under vacuum at 45°. Dissolve the resulting residue with 5.0 ml of the Solvent mixture. Prepare a blank solution from the blank solution corresponding to Solution S2.

Sample solution S2F. Evaporate 50.0 ml of Solution S2 to dryness under vacuum at 45°. Dissolve the residue with 5.0 ml of *methylene chloride*. Prepare a blank solution from the blank solution corresponding to Solution S2.

Reference solution (k). A 0.01per cent of *butylated hydroxy toluene RS*, 0.016 per cent of *polymer additive 02 RS*, 0.016 per cent of *polymer additive 03 RS*, and 0.016 per cent of *polymer additive 04 RS* in the solvent mixture.

Reference solution(l). A 0.016 per cent of *polymer additive 04 RS* and *0.016* per cent of *polymer additive 05 RS* in *methylene chloride.*

NOTE—Of the following reference solutions, prepare only those that are necessary for the analysis of the phenolic antioxidants stated in the composition of the substance to be examined.

Test A

Determine by liquid chromatography (2.4.14).

If the substance to be examined contains additive butylatedhydroxytoluene and/or additive ethylene bis[3,3-bis[3-(1,1dimethylethyl)-4-hydroxyphenyl]butanoate

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica microparticles (5 µm),
- mobile phase: a mixture of 70 volumes of *tetrahydrofuran,* 60 volumes of *acetronitrile*, and 10 volumes of *water,*
- flow rate: 1.5 ml per minute,
- spectrophotometer set at 280 nm,
- injection volume: 20 µl.

Inject reference solution (k).The test is not valid unless the resolution between the peaks due to *polymer additive 02 RS* and *polymer additive 03 RS* peaks is not less than 2.0 and the column efficiency is not less than 2500 theoretical plates calculated for *Butylated Hydroxytoluene RS.*

Inject Sample solution 12 corresponding blank solution, reference solution (k), Run the chromatogram for about 30 minutes. The peak areas of Sample solution 12 are less than the corresponding peak areas of reference solution (k).

NOTE—Sample solution S2E shows only peaks caused by antioxidants stated in the reference solution (k) and minor peaks that also correspond to the blank solution.

Test B

If the chromatogram obtained via Test A for Test solution S2E shows a peak with the same retention time as the last antioxidant eluted from Reference solution K.

Determine by liquid chromatography (2.4.14).

Chromatographic system

Carry out the test as described in Test A with the following modifications

- mobile phase: a mixture of 45 volumes *of 2 propanol* 50 volumes of *methanol* and 5.0 volumes of *water*,
- flow rate: 1.5 ml per minute.

Inject reference solution (l).The test is not valid unless the resolution between the peaks due to *polymer additive 04 RS* and *polymer additive 05 RS* peaks is not less than 2.0.

Inject Sample solution S2F corresponding blank solution, reference solution (l). The peak areas of Sample solution S2F are less than the corresponding peak areas of reference solution (l).

NOTE—Sample solution 13 shows only peaks caused by antioxidants stated in the reference solution (l) and minor peaks that also correspond to the blank solution.

B.3.2. Amides and Stearic Acid

Sample solution S2G: Evaporate 100 ml of Solution S2 to dryness under vacuum at 45°. Dissolve the resulting residue with 2.0 ml of acidified *methylene chloride*.

Reference solution (r) A 0.2 per cent of *stearic acid RS* prepared in *methylene*

Reference solution (s) A 0.08 per cent of *polymer additive 12 RS* prepared in *methylene chloride*

Reference solution (t) A 0.08 per cent of *polymer additive 13 RS* prepared in *methylene chloride.*

Test A

Determine by thin-layer chromatography(2.4.17), using the plate coated with *silica gel GF254.*

Mobile phase. a mixture of 75 volume of *trimethylpantane* and 25 volumes of *ethanol.*

Apply to the plate 10 µl of sample solution S2G, reference solution (r). Develop the plates over a path of 10 cm with mobile phase. After development, dry the plate in air and examine by spray with 2.0 per cent w/v 2, 6-dichlorophenol-indophenol sodium in dehydrated alcohol and heat in an oven at 120° for a few minutes to intensify the spots. Any spot corresponding to additive stearic acid in the chromatogram obtained with sample solution S2G is not more intense than the spot in the same position in the chromatogram of the corresponding reference solution (r).

Test B

Determine by thin-layer chromatography(2.4.17), using the plate coated with *silica gel GF254.*

Mobile phase A. Hexane.

Mobile phase B. A mixture of 95 volumes of *methylene chloride* and 5.0 volumes of *methanol.*

Apply to the plate 10 µl of sample solution S2G, reference solution (s) and reference solution (t). Develop the plates over a path of 13 cm with mobile phase A andover a path of 10cm with Mobile phase B respectively. After development, dry the plate in air and examine by spray with 40 per cent *phosphomolybdic acid* in *alcohol* heat in an oven at 120° for a few minutes to intensify the spots. Any spot corresponding to additive oleamide or erucamide in the chromatogram obtained with sample solution S2G is not more intense than the spot in the same position in the chromatogram of reference solution (s) and reference solution (t).

B.4. Related Substances (Residual Monomers / Residual Solvents)

B.4.1. Vinyl Acetate

Test solution: Place 0.25 to1.0 g of the test material into a 300 ml conical flask containing a magnetic stirrer. Prepare an extraction blank starting with an otherwise empty 300 ml conical flask. Add 40 ml of *xylene* and boil under a reflux condenser with stirring for 4 hours. After heating, continue stirring, allowing the solution to cool to the point that precipitation starts. Slowly add 25.0 ml of alcoholic *potassium hydroxide*. Boil again under a reflux condenser for 3 hours with continued stirring. While stirring, allow the solution to cool, rinse the condenser with 50.0 ml of water and add 30 ml of *0.05 M sulphuric acid* to the flask. Transfer the contents of the flask to a 400-ml beaker, rinsing the flask with the following: 2.0 volumes, 50.0 ml each, of a 200 g per litre solution of *anhydrous sodium sulphate* and 3.0 volumes, 20.0 ml each, of *water*. Add the rinsings to the flask.

Titrate the excess sulphuric acid in Test solution with *0.1 M sodium hydroxide*, determining the endpoint potentiometrically (2.4.25). Carry out a titration of the extraction blank.

Determine the amount of titrant (ml) required by subtracting the titrant volume used for the extraction blank (ml) from the titrant volume used for the extract (ml). Determine the amount of vinyl acetate by multiplying the volume of titrant required by the quantity 8.609 mg/ml. The content of vinyl acetate is calculated as:

$$\text{Content of vinyl acetate (weight per cent)} = \frac{\text{Amount of vinyl acetate (mg)}}{\text{Weight of material extracted (g)}} \times 10$$

Content of vinyl acetate

For containers. Not more than 25 per cent by weight.

For tubing. Not more than 30 per cent by weight.

B.5. Total organic carbon

The total organic content of Solution S1 is measured according to the general methodologies outlined in Total Organic Carbon (2.4.30).

The method used to perform the Total Organic Carbonanalysis should have a limit of detection of 0.2 mg per litre (ppm) and should have a demonstrated linear dynamic range from 0.2 to 20 mg per litre (which encompasses the TOC limit). A linear range with a higher upper concentration can be used if linearity is established. If sample extracts exceed this upper linear range, they must be diluted appropriately for analysis.

The difference between the sample and blank Total Organic Carbon concentrations is not more than 5 mg per litre.

B.6. Extractable Metals

Solution S3 is used for acid extractable metals.

Procedure for extract analysis

Instrumentation and methods are those specified in Elemental Impurities (2.3.13A).

All metals. Report the measured value in Solution S3 at values above 0.01 mg per litre (ppm), corresponding to 0.025 µg per g. If the measured values are below these values, report the result as less than 0.01 mg per litre (ppm), corresponding to less than 0.025 µg per g.

6.2.1.2.8. Polycarbonate (PC) Containers

A. Identification of Container Material

Test 1 – By FTIR Spectrophotometry (2.4.6)

Determine the infrared spectrum from 3800 cm^{-1} to 600 cm^{-1}. The specimen exhibits an absorption spectrum that is substantially equivalent to that of the *polycarbonate RS.* Substantial, as opposed to exact, equivalence allows for minor spectral differences arising from the natural compositional and/or physical variation among polymers of this class. Substantial equivalence is achieved when all differences between the sample andreferencespectra can be explained in the context of such natural compositional and/or physical variations.

Test 2 – By Differential Scanning Calorimetry (2.4.31)

Conduct the entire test under nitrogen. Heat the specimen from -20° to 150° at a heating rate between 2° and 10° per minutes. For protecting the instrument,rapidly cool the specimento room temperature. This thermogram is to be used for comparison.

Compare the thermogram of the specimen with that of the reference Polycarbonate. The glass transition temperature obtained from the thermogram of the specimen does not differ from that of the reference thermogram by more than 8.0°.

B. Chemical Tests

Preparation of Special Solutions for subsequent tests on Polycarbonate

Solution S1 (Water extraction)

Place 25 g of the test material in a borosilicate glass flask with a ground-glass neck. Add 500 ml of purified water, and boil under reflux conditions for 5 hours. Allow to cool to ambient temperature, and filter the extracting solution through a sintered-glass filter. Collect the filtrate in a 500 ml volumetric flask and dilute with purified water to volume; the diluted solution is *Solution S1.*

NOTE—Use Solution S1 within 4 hours of preparation.

Solution S2 (Acid extraction)

Place 5g in a borosilicate glass flask with a ground-glass neck. Add 100.0 ml of *0.1 M hydrochloric acid,* and boil under a reflux condenser for 1 hours with constant stirring. Allow to cool and the solids to settle, decant the solution into a 100.0 ml volumetric flask, and dilute to volume with *0.1 M hydrochloric acid*; the diluted solution is *Solution S2.*

Tests Using Special Solutions

B.1. Absorbance (2.4.7)

Determine the spectrum between 220 and 340 nm in Solution S1 Absorbanceshould be not more than 0.20

B.2. Acidity or alkalinity

To 100.0 ml of Solution S1 add 0.15 ml of *BRP indicator solution.* Determine the titration volume of *0.01M sodium hydroxide* required to change the colour of the indicator to blue. To a separate, 100.0 ml portion of Solution S, add 0.2 ml of *Methyl orange solution.* Determine the titration volume of *0.01 M hydrochloric acid* required to reach the beginning of the colour change of the indicator from yellow to orange.

Not more than 1.5 ml of *0.01 M hydrochloric acid* is required to reach the beginning of the colour change of the indicator from yellow to orange.

B.3. Related Substances (Residual Monomers / Residual Solvents)

B.3.1. Residual Solvents

By Head Space Gas Chromatography (2.4.13).

Test solution. Weigh 1.0 g of the test material and place it in a 20-ml headspace vial. Add 10.0 ml of *N, N,-dimethylformamide,* cap the vial closed, and sonicate for 4 hours. Cool to room temperature. Prepare a sample blank in a similar fashion.

Residual solvents primary solution. Weigh 500 mg each of *dichloromethane, toluene,* and *ethylbenzene*and 1250 mg of *chlorobenzene* into a 50.0 ml volumetric flask; dissolve and adjust with *N,N,-dimethylformamide* to volume.

Residual solvents stock solution. Transfer 5.0 ml of the Residual solvents primary solution into a 100.0 ml volumetric flask; adjust with *N, N-dimethylformamide* to volume.

Reference solutions. Pipet 0, 2, 3, 4, 5, and 6 ml of the Residual solvents stock solution into individual 100.0ml volumetric

flasks, dilute with *N-N-dimethylformamide* to volume and mix well. The six reference standards thus obtained (Reference solution blank and WS1 through WS5) contain, respectively, 0, 10, 15, 20, 25, and 30 mg per litre of *dichloromethane, toluene,* and *ethylbenzene* and 0, 37.5, 50, 62.5, and 75 mg per litre of *chlorobenzene.*

Chromatographic system

- a capillary column 30 m x 0.32 mm, packed with 100 per cent bonded and cross linked polyethylene glycol (5 µm),
- temperature:
  column: Start at 50°, hold for 20 minutes. Heat to 165° at 6° per minute, hold for 20 minutes,
- inlet port.140°,
- detector 250°,
- flame ionization detector
- flow rate: adjust to provide a constant pressure of 10 psi, using helium or nitrogen as carrier gas
- injection volume: 1 µl, split.

Head space conditions

- temperatures:
  thermostating: 115°,
  needle: 110°,
  transfer: 120°,
- thermostating: 60 minutes,
- pressurization, 0.5 minutes,
- injection, 0.1 minute,
- withdrawal, 0.2 minute,
- carrier gas pressure, 20 psi.

Conditioning. Inject the reference solution blank three times into the chromatographic system.

Inject reference solution WS3 five times into the chromatographic system. The test is not valid unless, the relative standard deviation of the peak areas in the chromatogram obtained with reference solution WS3 for is not less than 5.0 per cent. The symmetry factor for the caprolactam peak obtained for the third injection must be between 0.8 and 1.3.

Rinsing. Inject the Reference solution blank once.

Calibration, front of bracket. Inject each of the five Reference solutions once. Construct a linear calibration curve of the peak areas obtained for the Reference solutions versus their analyte concentrations for each analyte. The correlation coefficient (r^2) obtained for the best-fit linear regression line must be not less than 0.99.

Rinsing. Inject the Reference solution blank once.

Sample. Inject each test solution once, including the blank. Inject not more than six test solutions.

Rinsing. Inject Reference solution blank once.

Calibration, back of bracket. Inject each of the five Reference solutions once.

Calculations: Construct a linear calibration curve of the peak areas obtained for the Reference solutions versus their analyte concentrations (using the front and back of the bracket). The correlation coefficient (r^2) obtained for the best-fit linear regression line must be not more than 0.99. Calculate the amount of each analyte in the test solution by putting the peak area obtained for the test solution into the calibration curve.

Calculate the amount of each in the test material by multiplying this result by a factor of 10 and dividing the product by the weight of the test material in g, producing a result in µg per g.

$$\text{Analyte (}\mu g \text{ per g)} = \frac{\text{Analyte in sample solution (mg per litre)}}{\text{Weight of test material (g)}} \times 10$$

B.3.1. Bisphenol A

NOTE—Bisphenol A is monitored although it is a residual monomer and not an additive.

Test solution. Weigh 1.0 g of the test material and place it in a 250 ml round-bottom flask. Add 50.0 ml of *methylene chloride* and heat at 50° for 1.0 hour under a reflux condenser to dissolve the test material. Cool the solution to room temperature and slowly add 75 ml of *methanol* to the room temperature solution, with continuous stirring. Place in a refrigerator for 2 hours to cool the resulting solution. Filter the cooled solution through a sintered-glass filter. Wash the round-bottom flask and the filter twice with 15.0 ml of *methanol.* Evaporate the filtrate to dryness under vacuum at 45°. Dissolve the residue in 5.0 ml of *methylene chloride.* Add 0.5 ml of this solution and 0.5 ml of N,O-bis(trimethylsilyl)trifluoroacetamide to a 1.5-ml vial and close the vial immediately. Heat the closed vial at 40° for 2 hours and then cool to room temperature. Prepare a sample blank in a similar fashion.

Bisphenol A primary solution. Weigh 20 mg of *bisphenol A RS* in a 200.0 ml volumetric flask; dissolve and dilute with *methylene chloride* to volume.

Reference solutions. Pipet 0, 5, 10, 20, 30, and 40 ml of the BisphenolA primary solution into six 100.0 ml volumetric flasks. Dilute with *methylene chloride* to volume and mix well. The six reference standards thus obtained (Reference solution blank and WS1 through WS5) contain, respectively, 0, 5, 10, 20, 30, and 40 mg per litre of Bisphenol A.

Add 0.5 ml each of the Reference solutions and 0.5 ml of N,O-bis(trimethylsilyl)trifluoroacetamide to separate 1.5-ml vials and close the vials immediately. Heat the closed vials at 40° for 2 hours and then cool to room temperature.

Chromatographic system

- a capillary column 25 m x 0.25 mm, packed with 100 per cent dimethylpolysilxane (0.25 µm),
- temperature:
  column: 250°,
  inlet port detector 300°,
- flame ionization detector,

- flow rate: adjust to provide a constant pressure of 13 psi, using helium as carrier gas
- injection volume: 2 µl, split.

Head space conditions

- temperatures:
  thermostating: 115°,
  needle: 110°,
  transfer: 120°,
- thermostating, 60 minutes,
- pressurization, 0.5 minute,
- injection, 0.1 minute,
- withdrawal, 0.2 minute,
- carrier gas pressure, 20 psi.

Conditioning. Inject the reference solution blank three times into the chromatographic system.

Inject reference solution WS3 five times into the chromatographic system. The test is not valid unless, the relative standard deviation of the peak areas in the chromatogram obtained with reference solution WS3 for is not less than 5.0 per cent.

Rinsing. Inject the Reference solution blank twice.

Calibration, front of bracket: Inject each of the five Reference solutions once. Construct a linear calibration curve of the peak areas obtained for the Reference solutions versus their bisphenol A concentrations. The correlation coefficient (r2) obtained for the best-fit linear regression line must be not less than 0.98.

Rinsing. Inject the Reference solution blank once.

Sample. Inject each test solution once, including the Sample blank. Inject not more than six test solutions.

Rinsing. Inject the Reference solution blank once

Calibration, back of bracket: Inject each of the five Reference solutions once.

Calculations. Construct a linear calibration curve of the peak areas obtained for the Reference solutions versus their bisphenolA concentrations (front and back of bracket). The correlation coefficient (r2) obtained for the best-fit linear regression line must be not less than 0.98. Calculate the amount of bisphenol A in the Sample solution by putting the peak area obtained for the Sample solution into the calibration curve.

Calculate the amount of bisphenol A in the test material by multiplying this result by a factor of five and dividing the product by the weight of the test material in g, producing a result in µg per g,

$$\text{Bisphenol A (µµ per g)} = \frac{\text{Bisphenol A in test solution (mg per litre)}}{\text{Weight of test material}} \times 5$$

Not more than 100 µg per g.

B.4. Total organic carbon

The total organic content of Solution S1 is measured according to the general methodologies outlined in Total Organic Carbon (2.4.30).

The method used to perform the TOC analysis should have a limit of detection of 0.2 mg per litre (ppm) and should have a demonstrated linear dynamic range from 0.2 to 20 mg per litre (which encompasses the TOC limit). A linear range with a higher upper concentration can be used if linearity is established. If sample extracts exceed this upper linear range, they must be diluted appropriately for analysis.

The difference between the sample and blank Total Organic Carbon concentrations is not more than 5 mg per litre.

B.5. Extractable Metals

Solution S2 is used for acid extractable metals.

Procedure for extract analysis

Instrumentation and methods are those specified in Elemental Impurities (2.3.13A).

Arsenic, lead, cadmium, mercury, cobalt, nickel, and vanadium. Report the measured value in Solution S3 at values above 0.01 mg per litre (ppm), corresponding to 0.025 µg per g. If the measured values are below these values, report the result as less than 0.01 mg per litre (ppm), corresponding to less than 0.025 µg per g. Additional acceptance criteria for certain metals are provided as follows.

6.2.1.2.9. Polyamide-6 (PA-6) Containers

A. Identification of Container Material

Test 1 – By FTIR Spectrophotometry (2.4.6)

Determine the infrared spectrum from 3800 cm^{-1} to 600 cm^{-1}. The specimen exhibits an absorption spectrum that is substantially equivalent to that of the *polyamide-6 RS*. Substantial, as opposed to exact, equivalence allows for minor spectral differences arising from the natural compositional and/or physical variation among polymers of this class. Substantial equivalence is achieved when all differences between the sample andreferencespectra can be explained in the context of such natural compositional and/or physical variations.

Test 2 – By Differential Scanning Calorimetry (2.4.31)

Conduct the entire test under nitrogen. Heat the specimen from room temperature to 250° at a heating rate between 10 and 20°/minute and hold it for 1 minute. Cool the specimento room temperature at the highest cooling rate possible (typically, lower than a rate of 50° per minutes) and hold it for 1 minute. Reheat it to 250° at the same rate as adopted in the first heating.This reheat thermogram to be used for comparison.

Compare the thermogram of the sample with that of the reference Polyamide-6. The melting peak temperature obtained from the thermogram of the sample does not differ from that of the reference thermogram by more than 8.0°.

B. Chemical Tests

Preparation of Special Solutions for subsequent tests on Polyamide-6

Solution S1 (Water extraction)

Place 25 g of the test material in a borosilicate glass flask with a ground-glass neck. Add 500 ml of purified water, and boil under reflux conditions for 5 hours. Allow to cool to ambient temperature, and filter the extracting solution through a sintered-glass filter. Collect the filtrate in a 500 ml volumetric flask and dilute with purified water to volume; the diluted solution is *Solution S1*. Use *Solution S1* within 4 hours of preparation.

Solution S2 (Acid extraction)

Place 5 g in a borosilicate glass flask with a ground-glass neck. Add 100.0ml of *0.1M hydrochloric acid*, and boil under a reflux condenser for 1 hours with constant stirring. Allow to cool and the solids to settle, decant the solution into a 100.0 ml volumetric flask, and dilute to volume with *0.1M hydrochloric acid*; the diluted solution is *Solution S2*.

Solution S3 (Phenol extraction)

Dissolve 1.0 g of the test material in 50.0 ml of phenol by heating at 50° for 4 hours with constant stirring. This process produces *Solution S3*. Prepare a blank solution.

Tests Using Special Solutions

B.1. Absorbance (2.4.7)

Determine the spectrum between 220 and 340 nm in Solution S1.

Absorbanceshould be not more than 0.25

B.2. Acidity or alkalinity

To 100 ml of Solution S1 add 0.15 ml of BRP indicator solution. Determine the titration volume of *0.01 M sodium hydroxide* required to change the colour of the indicator to blue. To a separate, 100.0 ml portion of Solution S, add 0.2 ml of *methyl orange solution*. Determine the titration volume of *0.01 M hydrochloric acid* required to reach the beginning of the colour change of the indicator from yellow to orange.

Not more than 1.5 ml of *0.01 N sodium hydroxide* is required to change the colour of the indicator to blue.

Not more than 4.0 ml *of 0.01 N hydrochloric acid* is required to reach the beginning of the colour change of the indicator from yellow to orange.

B.3. Free Base Functions

Perchloric acid in 70 per cent phenol. Dissolve approximately 0.72 g (target 0.710–0.7250 g) of *perchloric acid* in 50.0 ml of phenol.

Titrate 50.0 ml of solution S3 with Perchloric acid in 70 per cent *phenol*, determining the end-point potentiometrically (2.4.25). Carry out a blank titration using phenol as extraction blank.

The difference between the titration volumes, extract versus extraction blank, is not more than 0.4 ml.

B.4. Related Substances (Residual Monomers/Residual Solvents)

B.4.1. Caprolactam

Determine by gas chromatography (2.4.13).

Test Solution. Dissolve 1.0 g of the test substance in sufficient quantity of *formic acid*. Dilute to 10.0 ml with same solvent.

Caprolactam primary solution. Dissolve 125 mg of *Caprolactam* reference in *formic acid* and dilute to 50.0 ml with same solvent.

Reference solutions. Pipet 0, 2, 4, 6, 8, and 10.0 ml of the Caprolactam primary solution into six 20.0 ml volumetric flasks. Dilute with anhydrous formic acid to volume. The six reference standards thus obtained (blank and WS1 through WS5) contain, respectively, 0, 250, 500, 750, 1000, and 1250 mg per litre of caprolactam.

Chromatographic system

- a capillary column 2 m x 4 mm, packed with silanized diatomaceous earth for gas chromatography impregnated with 10 per cent m/m of polyethylene glycol 20000,
- temperature:
  column. 170°,
  inlet port detector 250°,
- flame ionization detector
- flow rate 25 ml per minute, using helium or nitrogen as carrier gas,
- injection volume: 1 µl.

Inject 1 µl of the Reference solution blank three times into the chromatographic system.

Inject Reference solution WS4 five times into the chromatographic system. The test is not valid unless, the relative standard deviation of the peak areas in the chromatogram obtained with reference solution WS4 for is not less than 5 per cent. The symmetry factor for the caprolactam peak obtained for the third injection must be between 0.8 and 1.3.

Rinsing. Inject 1 µl Reference solution blank once.

Calibration, front of bracket. Inject each of the five Reference solutions once. Construct a linear calibration curve of the peak areas obtained for the Reference solutions versus their caprolactam concentrations. The correlation coefficient (r2) obtained for the best-fit linear regression line must be not less than 0.98.

Rinsing. Inject 1 µl the Reference solution blank once.

Sample. Inject 1 µl each test solution once. Inject not more than six test solutions.

Rinsing. Inject 1 µl Reference solution blank once.

Calibration, back of bracket. Inject 1 µl each of the five Reference solutions once.

Construct a linear calibration curve of the peak areas obtained for the Reference solutions versus their caprolactam concentrations (both front and back of bracket). The correlation coefficient (r2) obtained for the best-fit linear regression line must be not less than 0.98. Calculate the amount of caprolactam

in the test solution by putting the peak area obtained for the test solution into the calibration curve. Calculate the amount of caprolactam in the test material by multiplying this result by a factor of 10 and dividing the product by the weight of the test material in g, producing a result in weight per cent.

Not more than 1 per cent.

B.5. Total organic carbon

The total organic content of Solution S1 is measured according to the general methodologies outlined in Total Organic Carbon (2.4.30).

The method used to perform the Total Organic Carbon analysis should have a limit of detection of 0.2 mg per litre (ppm) and should have a demonstrated linear dynamic range from 0.2 to 20 mg per litre (which encompasses the Total Organic Carbon limit). A linear range with a higher upper concentration can be used if linearity is established. If sample extracts exceed this upper linear range, they must be diluted appropriately for analysis.

The difference between the sample and blank Total Organic Carbon concentrations is not more than 5 mg per litre.

B.6. Extractable Metals

Solution S2 is used for acid extractable metals.

Procedure for extract analysis

Instrumentation and methods are those specified in Elemental Impurities (2.3.13A)

Arsenic, lead, cadmium, mercury, cobalt, nickel, and vanadium. Report the measured value in solution S3 at values above 0.01 mg per litre (ppm), corresponding to 0.025 µg per g. If the measured values are below these values, report the result as less than 0.01 mg per litre (ppm), corresponding to less than 0.025 µg per g. Additional acceptance criteria for certain metals are provided as follows.

6.2.1.2.10. Polymer Additives

The polymer additive is given in Table 2.

6.2.1.3. Plastic Containers for Ophthalmic 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. Comply with the tests described under Plastic Containers for Parenteral Preparations (6.2.1.1).

Table 2 - Names of polymer additives with teir synonyms

Polymer Additive	Name of Polymer additive as per IUPAC Rules	Synonyms Name
Additive 01	(2*RS*)-2-ethylhexyl benzene-1,2-dicarboxylate	– **di(2-ethylhexyl) phthalate,** – 1,2-benzenedicarboxylic acid, bis(2-ethylhexyl) ester.
Additive 02	zinc (2*RS*)-2-ethylhexanoate	– **zinc octanoate,** – 2-ethylhexanoic acid, zinc salt (2:1), – zinc 2-ethylcaproate.
Additive 03	*N,N2* -ethylenedialcanamide (with *n* and *m* = 14 or 16)	– ***N,N'*-diacylethylenediamines,** – *N,N'*-diacylethylenediamine (in this context acyl means in particular palmitoyl and stearoyl).
Additive 04	EpoxidisedSoya Oil	
Additive 05	Epoxidised Linseed Oil	
Additive 06	(EINECS)/Pigment blue 29 (CI77007) ultramarine blue	
Additive 07	2,6-bis(1,1-dimethylethyl)-4-methylphenol	– **butylhydroxytoluene,** – 2,6-bis(1,1-dimethylethyl)-4-methylphenol, – 2,6-di-*tert*-butyl-4-methylphenol
Additive 08	ethylene bis[3,3-bis[3-(1,1-dimethylethyl)-4--hydroxyphenyl]butanoate]	– **ethylene bis[3,3-bis[3-(1,1-dimethylethyl)-4-hydroxyphenyl]butanoate],** – butanoic acid, 3,3-bis[3-(1,1-dimethylethyl)-4-hydroxyphenyl]-1,2-ethanediyl ester, – ethylene bis[3,3-bis(3-*tert*-butyl-4-hydroxy-phenyl) butyrate].

cont.

Polymer Additive	Name of Polymer additive as per IUPAC Rules	Synonyms Name
Additive 09	methanetetryltetramethyl tetrakis[3-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl] propanoate]	– **pentaerythrityl tetrakis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate],** – 2,2-bis[[[3-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl] propanoyl]oxy]methyl]propane- 1,3-diyl 3-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]propanoate, – benzenepropanoic acid, 3,5-bis(1,1-dimethyl-ethyl)-4-hydroxy-2,2-bis(hydroxymethyl) propane-1,3-diol ester (4:1), – 2,2-bis(hydroxymethyl)propane-1,3-diol tetrakis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl) propionate].
Additive 10	4,42 ,43 -[(2,4,6-trimethylbenzene-(1,3,5-triyl)tris methylene)]tris[2,6-bis (1,1-dimethylethyl)phenol]	– **2,22 ,23 ,6,62 ,63 -hexa-*tert*-butyl-4,42 ,43 -[(2, 4,6-trimethyl-1,3,5-benzenetriyl)trismethylene]triphenol,** – 1,3,5-tris[3,5-di-*tert*-butyl-4-hydroxybenzyl]-2,4,6-trimethyl-benzene, – phenol, 4,42 ,43 -[(2,4,6-trimethyl-1,3,5-benzenetriyl)tris (methylene)]tris[2,6-bis(1,1-dimethylethyl).
Additive 11	octadecyl 3-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]propanoate	– **octadecyl 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate,** – propanoic acid, 3-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-, octadecyl ester.
Additive 12	tris[2,4-bis(1,1-dimethylethyl)phenyl] phosphite	– **tris(2,4-di-*tert*-butylphenyl) phosphite,** – phenol, 2,4-bis(1,1-dimethylethyl)-, phosphite (3:1), – 2,4-bis(1,1-dimethylethyl)phenyl, phosphite.
Additive 13	1,3,5-tris[3,5-bis(1,1-dimethylethyl)-4-hydroxybenzyl]-1,3,5-triazine-2,4,6 (1*H*,3*H*,5*H*)-trione	– **1,3,5-tris(3,5-di-*tert*-butyl-4-hydroxybenzyl)-*s*-triazine-2,4,6(1*H*,3*H*,5*H*)-trione,** – 1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-trione, 1,3,5-tris[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methyl]-.
Additive 14	3,9-bis(octadecyloxy)-2,4,8,10-tetraoxa-3,9-diphosphaspiro[5.5]undecane	– **2,22 -bis(octadecyloxy)-5,52 -spirobi[1,3,2-dioxaphosphinane],** – 2,4,8,10-tetraoxa-3,9-diphosphaspiro[5.5]undecane, 3,9-bis(octadecyloxy)-.
Additive 15	1,12 -disulfanediyldioctadecane	– **dioctadecyl disulfide,** – octadecane, 1,12 -dithio-.
Additive 16	didodecyl 3,32 -sulfanediyldipropanoate	– **didodecyl 3,32 -thiodipropionate,** – didodecyl 3,32 -sulfanediyldipropanoate, – propanoic acid, 3,32 -thiobis-, dodecyl diester, – lauryl thiodipropionate.
Additive 17	dioctadecyl 3,32 -sulfanediyldipropanoate	– **dioctadecyl 3,32 -thiodipropionate,** – dioctadecyl 3,32 -sulfanediyldipropanoate, – propanoic acid, 3,32 -thiobis-, octadecyl diester, – stearyl thiodipropionate.
Additive 18	**Component I** 2,4-bis(1,1-dimethylethyl)phenyl biphenyl-4,4′-diyldiphosphonite **Component II** 2,4-bis(1,1-dimethylethyl)phenyl biphenyl-3,4′-diyldiphosphonite **Component III** 2,4-bis(1,1-dimethylethyl)phenyl biphenyl-3,3′-diyldiphosphonite **Component IV** 2,4-bis(1,1-dimethylethyl)phenyl biphenyl-4-ylphosphonite **Component V** 2,4-bis(1,1-dimethylethyl)phenyl phosphate **Component VI** 2,4-bis(1,1-dimethylethyl)phenyl 4′-[bis[2,4-bis(1,1-dimethylethyl)phenoxy] phosphanyl] biphenyl-4-ylphosphonate **Component VII** R-OH:2,4-bis (1,1-dimethylethyl)phenol	

Clarity of aqueous extract; Non-volatile residue. Comply with the tests described under Plastic Containers for Non-Parenteral Preparations (6.2.1.2.).

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 100 µL of a blank prepared as directed under Systemic injection test in one eye and 100 µL 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 100 µL of *sterile water for injection*. Hold the lid together for about 30 seconds. Instil in to the other eye 100 µL of the sample extract prepared as directed under Systemicinjection 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).

6.2.2. 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 3.

Table 3

Type of container	Test to be done
Type I and Type II glass containers to distinguish from Type III glass containers	Test 1 (surface test)
Type I and Type II glass containers where it is necessary to determine whether the high hydrolytic resistanceis due to the chemical composition or the surface treatment	Tests 1 and 2

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 4.

Table 4

Nominal capacity of container (ml)	Number of containers to be used	Volume of test solution to be used for titration (ml)
Up to 3	At least 20	25.0
5 or less	At least 10	50.0
6 to 30	At least 5	50.0
More than 30	At least 3	100.0

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°. 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 per cent 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° to 121° over 20 minutes, maintain a temperature of 121° for 60 minutes and reduce the temperature from 121° to 100° 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 0.15 ml of *methyl red solution* for each 50.0 ml of liquid. Titrate with *0.01 M 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 *0.01 M hydrochloric acid* required by the test solution. Calculate the volume of *0.01M hydrochloric acid* required for each 100.0 ml of test solution, if necessary. The result is not greater than the value stated in Table 5.

Table 5

Capacity of container [corresponding to 90 per cent average overflowvolume (ml)]	Volume of *0.01M hydrochloric acid* /100 ml of test solution	
	Type I or II glass(ml)	Type III glass(ml)
Not more than 1	2.0	20.0
More than 1 but not more than 2	1.8	17.6
More than 2 but not more than 5	1.3	13.2
More than 5 but not more than 10	1.0	10.2
More than 10 but not more than 20	0.80	8.1
More than 20 but not more than 50	0.60	6.1
More than 50 but not more than 100	0.50	4.8
More than 100 but not more than 200	0.40	3.8
More than 200 but not more than 500	0.30	2.9
More than 500	0.20	2.0

Test 2. Examine the number of containers indicated in Table 3. Rinse the containers twice with water and then fill completely with a 4 per cent 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 4. 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.

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 50.0 ml. Pipette 10.0 ml of the test solution from the combined contents of all the containers into a flask, add 10.0 ml of *nitric acid* and evaporate to dryness on a water-bath. Dry the residue in an oven at 130° for 30 minutes. Cool, add to the residue 10.0 ml 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 10.0 ml of *hydrazine-molybdate reagent* as the blank. The absorbance of the test solution does not exceed the absorbance obtained by repeating the determination using 0.1 ml of *arsenic standard solution (10 ppm As)* in place of the test solution (0.1 ppm).

6.2.3. Metal Containers

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 15° to 20°.

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 0.2 mm squares and note (a) the number of all metal particles 1mm in length and longer, (b) the number in the range 0.5 mm to less than 1mm and (c) the number in the range 0.2 mm 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.

Particles 1 mm and above	50
Particles 0.5 mm but less than 1 mm	10
Particles 0.2 mm but less than 0.5 mm	2
Particles less than 0.2 mm	Nil

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.

6.3. CLOSURES FOR CONTAINERS

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 polymerization - 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.

*NOTE 8—**Closures will follow the same tests as containers** Closures made from plastics will be governed by all requirements covered in 6.2.1. 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 shall be the responsibility of the user/manufacturer to ensure the compatibility of the pharmaceutical articles and stability of the product in the package system. Towards this the user / manufacturer shall have in place a system of quality assurance with the supplier / convertor to ensure compliance of the components of the package with the requirement stated in this chapter at all times. The user should take the "risk-based approach" to determine the testing and its frequency required to ensure this.

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 1 g to 2 g 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 per cent of the value obtained with the type sample (specimen).

Preparation of samples. Wash the closures by agitation in a 0.2 per cent 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 100 cm^2, in a suitable container of borosilicate glass or inert material, and add 200.0 ml of water per 100 cm^2, 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° to 123° 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 *waterfor injection.* Shake and immediately separate the solution from the closures by decantation (Solution A).

Prepare a blank in the same manner using 200.0 ml of *water for injection.*

Dry the treated closures at 64° to 66° 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 20.0 ml of solution A add 0.1 ml of *bromothymol blue solution.* Not more than 0.3 ml of *0.01 M sodium hydroxide* or 0.8 ml of *0.01 M 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 360 nm (2.4.7), using as the blank a solution prepared in the same manner as solution A but using 200.0 ml 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 20.0 ml of solution A, add 1ml of *1 M sulphuric acid* and 20.0 ml 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 0.25 ml of *starch solution,* added towards the end of the titration, as indicator. Repeat the operation using 20.0 ml of the blank prepared in the test for Light absorption. The difference between the titration volumes is not more than 7.0 ml.

Heavy Metals (2.3.13). 20.0 ml of solution A complies with the limit test for heavy metals, Method A.

Residue on evaporation. Evaporate 50.0 ml of solution A to dryness on a water-bath and dry at 105°. The residue weighs not more than 4.0 mg.

Volatile sulphides. Place closures, cut if necessary, with a total surface area of 20 ± 2 cm2 in a 100-ml conical flask and add 50.0 ml of a 2 per cent 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° 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 0.154 mg of *sodium sulphide* and 50.0 ml of a 2 per cent 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° to 14°) hypodermic needle with an external diameter of 0.8 mm (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 0.5 µm. 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 per cent w/v solution of *methylene blue* and reduce the external pressure by 27 kPa 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).

6.4. Labels on Container

6.4.1. Basic Statutes Governing Labelling

Requirements on Labelling of the packages/container for pharmaceuticals shall be governed as/the following provisions:

- Labelling requirements as/the Drugs & Cosmetics Act, 1940 and the Drugs & Cosmetics Rules, 1945 as amended from time to time.
- Section on Labelling covered in General Notices in the applicable version of the Indian Pharmacopoeia.

Annexure-A2

GOVERNMENT OF INDIA

Directorate General of Health Services
Central Drugs Standard Control Organization (CDSCO)
FDA Bhawan, Kotla Road, New Delhi

File No. 29/Misc./38/2019-DC **Dated:** 27-01-2020

To,

Dr. AC Mishra
Joint Director (Standards)
Food Safety and Standards Authority of India
Ministry of Health and Family Welfare
FDA Bhawan, Kotla Road
New Delhi-110002
India.

Subject: Action Taken Report on NGT report- Regarding.

Sir,

Please refer to your letter dated no. 1-95/stds/Misc/SP(L&C/A)/FSSAI-2015(pt-4) dated 05.11.2019 on the subject noted above.

It may be mentioned that the report of Dr. M.K Bhan committee, constituted by the Ministry of Health and Family Welfare to review the safety of Polyethylene terephthalate (PET) and its containers for the packaging of pharmaceuticals was submitted before the Hon'ble NGT.

Considering the recommendations of the committee, Indian Pharmacopoeia Commission (IPC) constituted a committee in June 2016 under the Chairmanship of Dr. Y.K Gupta with members from IPC, PET industry, pharmaceutical industry and domain experts from other Government Institutes as constituents.

On the basis of the recommendation of the above committee, IPC has taken action on the Chapter 6 of Indian Pharmacopoeia (IP) 2014 for revision and accordingly revised & updated the Chapter 6, **"Primary Packages for Pharmaceutical Articles"** and same has been published in Indian Pharmacopoeia (IP) 2018. It includes standards of PET (Polyethylene terephthalate) as well as standards of other polymers/plastic containers and primary packaging of pharmaceuticals.

Details in this regard as received from IPC, Ghaziabad is enclosed for your reference.

Yours faithfully,

(Dr. V.G Somani)
Drugs Controller General (India)

Copy to:

1-Office of DGHS, Nirman Bhawan
2-IPC, MoH&FW, Sector-23, Rajnagar, Ghaziabad-201002

Enclosure: IPC letter no. T.17011/01/2018-AR&D

---TRUE COPY---

Phone No. : +91-120-2783400, 2783401
Fax No. : +91-120-2783311
E-Mail : lab.ipc@gov.in
Website : www.ipc.gov.in

INDIAN PHARMACOPOEIA COMMISSION

(Ministry of Health & Family Welfare, Government of India)
Sector 23, Raj Nagar, Ghaziabad 201 002

F.No. T.17011/01/2018-AR&D Dated: 24th January, 2020

To,
Drugs Controller General (India)
Central Drugs Standard Control Organization
FDA Bhawan, Kotla Road
New Delhi 110002

Subject: Report of expert committee to examine "whether any further regulatory action is required on the subject of restrictions on the packaging by use of plastic material, after steps already taken and if so to what extent"

Respected Sir,

This has the reference to your letter F.No. 12-01/19-DC (Pt-164) dated 06.01.2020 and our letter F.No. T.17011/01/2018-AR&D dated 16.01.202 on the subject mentioned above. In August 2015, Ministry of Health and family Welfare, Government of India constituted a High Level Committee (HLC) under the chairmanship of Prof. M.K. Bhan to review the safety of Polyethylene Terephthalate (PET) and its containers for the packaging of pharmaceuticals. This HLC concluded that while PET containers are safe for the packaging of pharmaceuticals, the Indian Pharmacopoeia (IP) needs to be updated to include guiding standards for PET.

In this regard, to fulfill the requirement of the HLC, the Indian Pharmacopoeia Commission constituted a committee in June 2016 under the chairmanship of Prof. Y.K. Gupta with members from IPC, PET industry, pharmaceutical industry and domain experts from other government institutes as constituents.

The basis of the recommendations of the Committee, IPC has taken the action on the chapter "6. Containers" of Indian Pharmacopoeia 2014 for revision and accordingly revised and updated the chapter has been published in IP-2018. The high lights of revisions in the chapter are as below:

1. The chapter is entitled as "6. PRIMARY PACKAGES FOR PHARMACEUTICAL ARTICLES".
2. The chapter has four parts Introduction, Containers, Closures and Labelling.
3. The biological tests (*in vitro* (2.2.23) and *in vivo* (2.2.24)) on plastic containers are also included.
4. PET Containers for primary packaging of drug formulations was included under section 6.2.1.2.1.
    - The section contains Definition, Production of PET resin and Quality assessment of PET containers (Identification by FTIR spectroscopy, UV spectroscopy and DSC)
    - Chemical tests by using special solutions S1 (Water extraction), S2 (Ethanol extraction), S3 (Acid extraction), S4 (Alkali extraction), appearance of solution,

Extractable metals such as Barium, Cobalt, Manganese, Titanium, Zinc, Antimony, Related substance (Residual monomers/Residual Inorganics), Total terephthalyol moieties, Ethylene glycol .

5. Labels on Containers are revised to meet the requirements of Drugs and Cosmetics Act 1940 and Rules there under.
6. A flow diagram explaining the route to deciding about the suitability of a plastic container has been introduced as a unique feature.
7. Alignment with the latest version of British Pharmacopoeia, European Pharmacopoeia, United States Pharmacopoeia and a linkage with the relevant BIS Standards.

Accordingly, the chapter "6. Primary Packages for Pharmaceutical Articles" has been harmonized at par with other global Pharmacopoeias.

Thanking you,

Yours faithfully

(Dr. Jai Prakash) 24/01/2020
Secretary-cum-Scientific Director (I/c)

Gmail

51

Kirtiman Singh <kirtimansingh.office@gmail.com>

ADVANCE SERVICE OF ADDITIONAL AFFIDAVIT IN OA NO. 15/2014- HIM JAGRITI UTTRANCHAL WELFARE SOCIETY VS UNION OF INDIA

1 message

Kirtimansinghoffice <kirtimansingh.office@gmail.com> Wed, Jan 6, 2021 at 3:49 PM
To: litigation.life@gmail.com, aodelhi@fssai.gov.in

Dear Sir,

Please find attached additional affidavit.

--

Regards,

Kirtiman Singh

Office:- A-9, Basement
South Extension Part-I
New Delhi – 110049
Phone:-011-49071872

ADDITIONAL AFFIDAVIT DATED 12.11.2020.pdf
4592K