BUREAU OF INDIAN STANDARDS

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भारतीय मानक मसौदा

होम्योपैथिक औषधि के निर्माण, पैकेजिंग और वितरण हेतु प्लास्टिक कंटेनर व क्लोज़र – विशिष्टि

Draft Indian Standard

Plastic Containers and Closures for Packaging & Dispensing of Homoeopathic Medicine - Specification

Homoeopathy Sectional Committee, AYD 07 **Last Date of Comments: 14-01-2024**

FOREWORD

Plastics are the polymers of synthetic or semisynthetic organic substances resulting from the process of polymerization. The process of polymerization continues even after formation of desired polymer, which means that we have been using Plastic containers, the constituents of which have never seized to react among themselves. Moreover, very little or almost nothing is known about the numerous individual chemicals used in manufacturing plastics. Due to the leaching properties of Plastics, the U.S. F.D.A. had classified Plastics as "Indirect Additives" which means that though they are not directly added to the substance stored in them, they seep into the contained substances.

Any Packaging materials must not interact physically or chemically with a packaged article in a manner that causes its safety, identity, strength, quality, or purity to fail to conform to established requirements. Any plastic material used to construct a *Packaging system* must meet the applicable requirements of *Plastic Materials of Construction* confirming to USP 659 and 661.

Being cost-effective and user-friendly, plastic containers and closures are widely used in Manufacturing, Primary packaging and dispensing of Homoeopathic medicines by the industry, dispensing chemists, and clinics. It is easily moldable in different shapes and shatter proof. The leaching effect is a matter of concern for long storage and dispensing, it may not be safe and contaminate the medicine. There is a high demand of standards for the material used in the preparation of these plastic containers and closures used in Homoeopathy.

For standardization of plastic material used in the preparation of phials, droppers, stoppers, caps, bottles, container for manufacturing purpose and their testing procedure, references from Indian Standards as well as United State Pharmacopoeia have been taken, as it is widely accepted among the pharmaceutical industries. Also, due consideration has been given to the provisions of the Drug and Cosmetics Act, 1940 and Rules framed thereunder. However, this standard is subject to the restrictions imposed under these Rules and Regulations, wherever applicable.

Draft Indian Standard

Plastic Containers and Closures for Packaging & Dispensing of Homoeopathic Medicine - Specification

1 SCOPE

This standard prescribes the requirements, methods of sampling and testing of Plastic containers and closures used in Packaging & Dispensing of Homoeopathic Medicines. Provision regarding specifications for plastic Phials, Bottles, Droppers, Stoppers, Caps, and Manufacturing containers are also included.

2. REFERENCES

The standards below contain provisions that may be applied here as suitable. At the time of publication, the editions indicated were valid. All standards are subject to revision, and parties to agreements based on this standard are encouraged to investigate the possibility of applying the most recent editions of these standards.

IS No.	Title
IS 9833:1981	List of Pigments and Colorants for use in Plastics in contact with Foodstuffs, Pharmaceuticals, and Drinking Water
IS 9845:1998	Determination of overall Migration of constituents of Plastics Materials and Articles Intended to Come into Contact with Foodstuffs – Method of Analysis
IS 16738:2018	Positive list of constituents for polypropylene, polyethylene and their copolymers for its safe use in contact with foodstuffs and pharmaceuticals
IS 10146:1982	Specification for Polyethylene for its Safe Use in Contact with Foodstuffs, Pharmaceuticals, and Drinking Water.
IS 7408: (Part 1) :2000	Blow Moulded Polyolefin Containers Specification
IS 2828: 2001	Plastics – Vocabulary (Second Revision)
IS 7019:1998	Glossary of Terms in Plastics and Flexible Packaging, Excluding Paper
IS 2798:1998	Methods of Test for Plastics Containers
IS 2530:1963	Methods for Test for Polyethylene Molding Materials and Polyethylene
IS 12252:1987	Specification for Polyalkylene Terephthalates (PET and PBT) for Their Safe Use in Contact with Foodstuffs Pharmaceuticals and Drinking Water

IS 12229:1987	Positive List of Constituents of Polyalkylene Terephthalates (PET And PBT) For Their Safe Use In Contact With Foodstuffs, Pharmaceutical And Drinking Water
IS 13193:1992	Polyalkylene Terephthalates (PET and PBT) for Moulding and Extrusion- Specification
IS 10910:1984	Specification for polypropylene and its copolymers for its safe use in contact with foodstuffs, pharmaceuticals and drinking water
Is 10951:2002	Polypropylene Materials for Moulding and Extrusion (First Revision)
Is 10909:2001	Positive List of Constituents of Polypropylene and Its Copolymers in Contact With Foodstuffs, Pharmaceuticals and Drinking Water
IS 7328: 2020	Specification for Polyethylene Material for Moulding and Extrusion (Third Revision)
IS 1108: 1975	Specification for Pharmaceutical Glass Containers-(Second Revision)
USP 661	Plastic Packaging Systems and Their Materials of Construction
USP 661.1	Plastic Materials of Construction
USP 661.2	Plastic Packaging Systems for Pharmaceutical Use
USP 659	Packaging and Storage Requirements
IP 2022 (Chapter 6)	Indian Pharmacopoeia
FSS-2018	Food Safety and Standards (Packaging) Regulations, 2018
IS 3025: 1987	Methods Of Sampling And Test (Physical And Chemical) For Water and Wastewater
IS 8688:2004	Plastic Bottles for Potable Water-Specification (Second revision)
IS 4905:2015	Random Sampling and Randomization Procedures
IS 14534:2023	Plastics Recovery and Recycling of Plastics Waste — Guidelines

3. TERMINOLOGY/DEFINITIONS

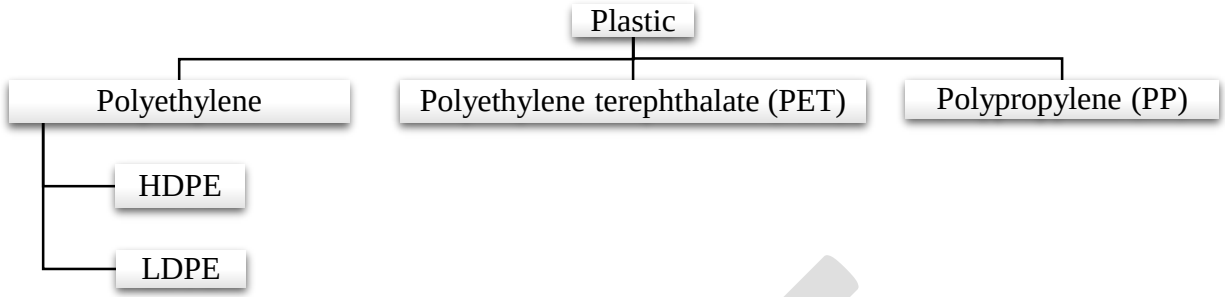
For this standard the definitions given in IS 2828 and IS 7019 shall apply.

Container: A receptacle that holds an intermediate compound, Active Pharmaceutical Ingredient (API), excipient, or dosage form, and is in direct contact with the article (e.g., vials, bottles, phials, syringes, and pen injectors).

Closure: A material that seals an otherwise open space of a *Container* and provides protection for the contents. It also provides access to the contents of the *Container* (e.g., screw caps and stoppers).

4. REQUIREMENTS

The homoeopathic pharmaceutical industries must ensure that the Certificate of Analysis (COA) of containers and closures shall comply with the following requirements (wherever applicable):



4.1 Basic Resins:

4.1.1 Resins for Phials- Plastic phials shall be manufactured by using High density polyethylene (HDPE).

For the manufacturing of Plastic Phials, the standards of IS 16738- Positive list of constituents for polypropylene, polyethylene and their copolymers for its safe use in contact with foodstuffs and pharmaceuticals, IS 7328 -High Density Polyethylene Materials for molding and extrusion-specification, and IS 10146- Specification for Polyethylene for its Safe Use in Contact with Foodstuffs, Pharmaceuticals, and Drinking Water, shall apply.

4.1.2 Resins for Bottles- Plastic bottles shall be manufactured by using Polyalkylene terephthalates (PET), High-density polyethylene (HDPE) or Polypropylene (PP).

Polyalkylene terephthalates (PET) Bottles: For the manufacturing of Plastic Bottles from Polyalkylene terephthalates (PET), the standards described in IS 12252- Specification for Polyalkylene Terephthalates for their Safe Use in Contact With Foodstuffs Pharmaceuticals and Drinking Water, IS 12229- Positive List of Constituents of Polyalkylene Terephthalates (PET and PBT) For Their Safe Use In Contact With Foodstuffs, Pharmaceutical And Drinking Water, IS 13193- Polyalkylene Terephthalates (PET and PBT) for Moulding and Extrusion- Specification and IS 7408 (Part-1)- Blow Molded Polyolefin Containers Specifications, shall apply.

High-Density Polyethylene (HDPE) Bottles: For the manufacturing of Plastic Bottles from High-density polyethylene (HDPE), the IS given above in **4.1.1** for High-density polyethylene (HDPE) Phials and IS 7408 (Part-1)- Molded Polyolefin Containers Specifications, shall apply.

Polypropylene (PP) Bottles: For the manufacturing of Plastic Bottles from **Polypropylene (PP)**, the IS 10910- Polypropylene and its Copolymers for its Safe Use in Contact With Foodstuffs, Pharmaceuticals and Drinking Water, IS 10951- Polypropylene Materials for Moulding and Extrusion (First Revision), IS 10909- Positive List of Constituents of Polypropylene and its Copolymers in Contact With Foodstuffs, Pharmaceuticals and Drinking Water and IS 7408 (Part-1)- Blow Molded Polyolefin Containers Specifications, shall apply.

The nominal capacities of the bottles shall be 90% of overflow capacity *(Note: where nominal capacity is the maximum that can be filled and not the net quantity of the container):*

The nominal capacity of a bottle indicates the quantity of liquid which a bottle of average wall thickness shall contain when the bottle is filled to the turn of the shoulder.

The bottle shall pass the drop impact test as prescribed in IS 2798.

4.1.3 Resins for Plastic Jars- Plastic jars used for the purpose of storing biochemic tablets in homoeopathic pharmaceutical industries shall be prepared by using Polyalkylene terephthalates (PET), or High-density polyethylene (HDPE).

Polyalkylene terephthalates (PET) Jars: For the manufacturing of Plastic Jars from Polyalkylene terephthalates (PET), the standards given above in **4.1.2** for Polyalkylene terephthalates (PET) Bottles, shall apply.

High-density polyethylene (HDPE) Bottles: For the manufacturing of Plastic Jars from High-density polyethylene (HDPE), the standards given above in **4.1.1** for High-density polyethylene (HDPE) Phials and IS 7408 (Part-1)- Molded Polyolefin Containers Specifications, shall apply.

Plastic Amber colored Jars are used in Homeopathy for the dispensing and sale of Homeopathic tablets.

4.1.4 Resins for manufacturing purpose plastic containers- Plastic containers used for the purpose of manufacturing in homoeopathic pharmaceutical industries shall be prepared by using High density polyethylene (HDPE).

For this purpose, the standards given above in **4.1.1** for High-density polyethylene (HDPE) Phials and IS 7408 (Part-1)- Molded Polyolefin Containers Specifications, shall apply.

4.1.5 Resins for Caps-Plastic caps shall be prepared by using High density polyethylene (HDPE) or Polypropylene (PP) material.

High-density polyethylene (HDPE) Caps: For the manufacturing of Plastic Caps from High-density polyethylene (HDPE), the standards given above in **4.1.1** for High-density polyethylene (HDPE) Phials, shall apply.

Polypropylene (PP) Caps: For the manufacturing of Plastic Caps from Polypropylene (PP), the standards given above in **4.1.2** for Polypropylene (PP) Bottles, shall apply.

4.1.6 Resins for Stoppers-Plastic Stoppers shall be prepared by using Low density polyethylene (LDPE).

For the manufacturing of Plastic Stoppers from Low density polyethylene (LDPE), the IS 16738-Positive list of constituents for polypropylene, polyethylene and their copolymers for its safe use in contact with foodstuffs and pharmaceuticals, and IS 7328 -High Density Polyethylene Materials for

molding and extrusion- specification, and IS 10146- Specification for Polyethylene for its Safe Use in Contact with Foodstuffs, Pharmaceuticals, and Drinking Water, shall apply.

Stoppers shall form a liquid-tight seal with the bottle neck.

4.1.7 Resins for Droppers-Plastic droppers shall be prepared by using Low density polyethylene (LDPE).

For the manufacturing of Plastic Droppers from Low density polyethylene (LDPE), the standards given above in **4.1.6** for Low density polyethylene (LDPE) Stoppers, shall apply.

Dropper insert flow rates refer to the speed at which droplets are dispensed. The first drop dispensed shall take 2 to 5 seconds and after that, it shall take 1 to 3 seconds.

Droppers shall form a liquid-tight seal with the bottle neck.

4.2 Workmanship:

4.2.1 The material shall comply with the threshold limits of the manufacturing residues polymerization ingredients auxiliary items as prescribed in IS 16738- Positive list of constituents for polypropylene, polyethylene and their copolymers for its safe use in contact with foodstuffs and pharmaceuticals, IS 12229- Positive List of Constituents of Polyalkylene Terephthalates (PET And PBT) For Their Safe Use In Contact With Foodstuffs, Pharmaceutical And Drinking Water and IS 10909- Positive List of Constituents of Polypropylene and its Copolymers in Contact With Foodstuffs, Pharmaceuticals and Drinking Water.

4.2.2 Pigments and Colorants - In case the colorants and pigments used, they shall comply with the list and limits of the pigments and colorants prescribed in IS 9833-List of Pigments and Colorants for use in Plastics in contact with Foodstuffs, Pharmaceuticals, and Drinking Water.

4.2.3 All above containers and closures shall be manufactured by a suitable process adhering to good manufacturing practice (GMP).

4.2.4 Nominal Capacity and Overflow capacity to be determined as per IS 1108- Specification for Pharmaceutical Glass Containers.

4.2.5 The brimful capacity of the bottle shall exceed the normal capacity by a minimum of 5%. The brimful capacity shall be determined by the method prescribed in IS 2798- Methods of Test for Plastics Containers.

4.2.6 All containers shall be thoroughly cleaned immediately before filling by automatic/semi-automatic washing machines. Washing shall be accomplished by pre-rinse and final rinse. For final rinse DM water/Purified water shall be used. Bottles should be thoroughly drained after final rinse so that strength of medicine is not affected after filling.

4.2.7 After the final rinse, containers shall be air dried or vacuum dried properly.

5. TESTING PROCEDURE

Homoeopathic pharmaceutical industries shall ensure that the containers procured by them are in compliance with the below testing parameters. A certificate of analysis with these parameters from the plastic manufacturing companies can be accepted for this purpose.

5.1. POLYETHYLENE

Polyethylene Molding Materials shall be tested as given in IS 2530- Methods for Test for Polyethylene Molding Materials and Polyethylene.

A. Identification of type of Polyethylene (by IR/ Differential scanning)

5.1.1 HDPE Containers

5.1.1.1 Infrared Spectroscopy— Determine the infrared spectrum from 3800 cm−1 to 650 cm−1 (2.6–15 mm). The specimen exhibits an absorption spectrum that is substantially equivalent to that of USP High-Density Polyethylene 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 and Reference Standard spectra can be explained in the context of such natural compositional and/or physical variations.

Methodology (USP 661.1)

Apparatus: Use an infrared spectrophotometer capable of correcting for the blank spectrum and able to measure in transmission mode or equipped with an internal reflectance accessory and an appropriate internal reflectance plate.

Sample preparation

Transmission mode—Prepare a specimen of appropriate thickness (polyethylene about 250 mm; polypropylene about 100 mm) without visible defects (cracks or holes). The specimens can be compressed to form a thin, uniform film by exposure to elevated temperatures and pressures (2000 psi or more). The temperatures at which the thin films are generated represent a trade-off between producing a melt (which dictates the lowest temperature necessary) and degrading the sample (which dictates the highest temperature allowed). Ultimately, the temperatures that are used are appropriate if the film produced is conducive to the IR analysis.

Internal reflectance mode—Prepare a flat section, and trim it as necessary to obtain a segment that is convenient for mounting in the internal reflectance accessory. Taking care to avoid scratching the surfaces, wipe the specimen with dry paper or, if necessary, a soft cloth dampened with methanol, and permit the surfaces to dry. Before mounting the specimen on the plate, compress it to form a thin, uniform film by exposure to elevated temperatures under high pressure (2000 psi or more). Then securely mount the specimen on the internal reflection plate, ensuring adequate surface contact.

Procedure: Place the mounted specimen sections in the sample compartment of the infrared spectrophotometer or the internal reflectance accessory and place the assembly in the specimen beam of the infrared spectrophotometer. For internal reflectance, adjust the specimen position and

mirrors within the accessory to permit maximum light transmission of the unattenuated reference beam. (For a double-beam instrument, attenuate the reference beam after completing the adjustment in the accessory to permit full-scale deflection during the scanning of the specimen.)

5.1.1.2 Differential Scanning Calorimetry *(IP 2022/USP 661.1)*

Sample preparation: 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].

Procedure: 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° per minute and hold it for 1 minute. Cool the specimen to 40° at the same rate adopted for heating and 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°.

5.1.2 LDPE Containers

5.1.2.1 Infrared spectrophotometry—Determine the infrared spectrum from 3800 cm−1 to 650 cm−1 (2.6–15 mm). The specimen exhibits an absorption spectrum that is substantially equivalent to that of the USP Low-Density Polyethylene 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 and Reference Standard spectra can be explained in the context of such natural compositional and/or physical variations.

Methodology – Same as in HDPE (USP 661.1)

5.1.2.2 Differential scanning calorimetry (IP 2022/USP 661.1):

Sample preparation: 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].

Procedure: 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° per minute and hold it for 1 minute. Cool the specimen to 40° at the same rate adopted for heating and 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 Test

Preparation of special solutions for Various Chemical Tests (physiochemical tests, polymer additives, migration, and functionality tests):

Table 1

Extractions Performed for Various Chemical Tests			
Extraction / Solutions	**Extracting solvent**	**Polyethylene/ Polypropylene PPE**	**PET**
S1	Water	Absorbance, Acidity/alkalinity, Total organic carbon	Absorbance, Acidity/alkalinity, Total organic carbon
S2	Toluene	Phenolic antioxidants, nonphenolic, antioxidants, amides, and stearates	NA
S3	Acid	Extractable metals	Extractable metals
S4	Alkali	NA	Extractable metals: Sb and Ge
S5	Alcohol	NA	Absorbance

B.1. Physicochemical test (for both HDPE/LDPE)- (Reference USP 661.1/ IP-2022):

Preparation of Solution S1 (Water extraction): Place 25 g of the test material in a borosilicate glass flask with a round glass neck. Add 500 mL of Purified Water, and boil under reflux conditions for 5 h. Allow to cool 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 designated Solution S1.
(Note: Use Solution S1 within 4 h of preparation)

B.1.1. Appearance of solution: Solution S1 is clear and colourless.

B.1.2. Absorbance: Determine the spectrum between 220 nm and 340 nm in Solution S1. Absorbance should be Not more than 0.2.

B.1.3. 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 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 0.01M sodium hydroxide is required to change the colour of the indicator to blue.

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

BRP indicator solution: 1.0 mg/mL of bromothymol blue, 0.2 mg/mL of methyl red, and 0.2 mg/mL of phenolphthalein in alcohol. Filter the resulting solution.

Methyl orange solution: Dissolve 100 mg of methyl orange in 80 mL of Purified Water and dilute with alcohol R to 100 ml. Test for sensitivity: Add 0.1 mL of Methyl orange solution to 100 mL of carbon dioxide–free Purified Water. NMT 0.1 mL of 1 N hydrochloric acid is required to change the colour from yellow to red.

B.1.4. *Total organic carbon:*

The total organic content of *Solution S1* is measured according to the general methodologies outlined in *Total Organic Carbon (IP- 2.4.30 / USP 643).* 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. 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 TOC concentrations is NMT 5 mg/L.

B.2. Polymer Additives (Ref. IP 2022/ USP 661.2)

Plastics may contain other substances such as residues from the polymerization process and additives such as plasticizers, stabilizers, antioxidants, pigments, and lubricants.
These tests should be carried out in whole or in part as required due to the stated composition of the material.

Preparation of Solution S2 (Toluene extraction**):** Place 2.0 g of the test material in a 250-mL borosilicate glass flask with a round-glass neck. Add 80 mL of toluene and boil under a reflux condenser for 1.5 h, stirring constantly. Allow to cool to 60° and add, with continued stirring, 120 mL of methanol. Pass the resulting solution through a sintered-glass filter. Rinse the flask and the filter with 25 mL of a mixture of 40 mL of toluene and 60 mL 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.

B.2.1. Phenolic Antioxidant

Solvent mixture: Mixture of equal volumes of acetonitriles 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 50.0ml of Solution S2 to dryness under vacuum at 45°. Dissolve the residue with 5.0 ml of dichloromethane. 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: 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 solution containing 0.01% w/v of butylated hydroxyl toluene IPRS and 0.024% w/v of polymer additive 01 IPRS in the solvent mixture.
Reference solution (b): A solution containing 0.024 %w/v, each of, *polymer additive 02 IPRS* and *polymer additive 03IPRS* in the solvent mixture.
Reference solution *(c):* A solution containing 0.024 per cent w/v, each of, *polymer additive 04 IPRS* and *polymer additive 05 IPRS* in *dichloromethane.*
Reference solution (d): A 0.01 per cent w/v solution of *butylated hydroxytoluene IPRS* in the solvent mixture.
Reference solution (e): A 0,024 per cent w/v solution of *polymer additive 01 IPRS* in the solvent mixture.
Reference solution (f): A0.024 per cent w/v solution of *polymer additive 06 IPRS* in the solvent mixture.
Reference solution (g): A 0.024 per cent w/v solution of *polymer additive 02 IPRS* in the solvent mixture.
Reference solution (h): A 0.024 per cent w/v solution of *polymer additive 03 IPRS* in the solvent mixture.
Reference solution (i): A 0.024 per cent w/v solution of *polymer additive 04 IPRS* in *dichloromethane.*
Reference solution (j): A 0.024 per cent w/v solution of *polymer additive 05 IPRS* in *dichloromethane.*
(Note: The nature and amount of additives (plasticizers, stabilizers, antioxidants, pigments, and lubricants.) in the plastics used for packaging systems are dictated by the type of polymer, the polymer's use, and the process used to convert the polymer into components, containers, or packaging systems).

Selection of Test method is based on the nature of additives, used to prepare plastic material.

Test A
If the substance to be examined contains **additive butylated hydroxyl toluene and/or additive ethylene bis [3,3-bis [3-(I, ldimethylethyl)-4-hydroxyphenyl] butanoate**

Determine by liquid chromatography
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 per minute,
- spectrophotometer set at 280 nm,
- injection volume: 20 pl.
-Inject reference solution (a). The test is not valid unless the resolution between the peaks due to additive butylatedhydroxytoluene and 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 tertbutyl-4-hydroxyphenyl) propionate; 2,2,23 ,6,6,63 -hexa-tcrtbutyl-4,4,43 -[(2,4,6-trimethyl-l,3,5-benzene-triyl) trismethylene] triphenol; octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionate; tris (2,4-di-tert-butylphenyl) phosphite; l,3,5-tris (3,5-di-tert-butyl-4-hydroxybenzyl)-striazine-2,4,6 (177,3//,577)-trione**

Determine by liquid chromatography
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-trimethyl4,3,5-benzene4riyl) 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
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 octadecyi-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.2.2. Non-phenolic Antioxidant

Determine by TLC
Mobile phase A: Hexane
Mobile phase B: Dichloromethane

Dichloromethane, acidified: To of dichloromethane 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 *dichloromethane* acidified.

Reference solution (m): A 0.6 per cent w/v solution of *polymer additive 08 IPRS* in *dichloromethane.* Dilute 2.0 ml of the solution with *dichloromethane,* acidified to 10 ml.
Reference solution (n): A 0.6 per cent w/v of *polymer additive, 09 IPRS* in *dichloromethane.* Dilute 2.0 ml of the solution with *dichloromethane,* acidified to 10.0 ml.
Reference solution (o): A 0.6 per cent w/v solution of *polymer additive 10 IPRS* in *dichloromethane.* Dilute 2.0 ml of the solution with *dichloromethane,* acidified to 10.0 ml.
Reference solution (p): A solution containing 0.6 %w/v, each of, *polymer additive 10 IPRS* and *polymer additive 09 IPRS* in *dichloromethane.* Dilute 2.0 ml of the solution with *dichloromethane,* 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 spots. 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.2.3. Amides and Stearates

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

Reference solution (r): A 0.2 percent w/v solution of *stearic acid IPRS* in *dichloromethane.*
Reference solution (s): A 0.2 percent w/v solution of *polymer additive 12 IPRS* in *dichloromethane.*
Reference solution (t): A 0.2 percent w/v solution of *polymer additive 13 IPRS* in *dichloromethane.*

Test A

TLC, using the plate coated with silica *gel GF254*

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

After development, dry the plate in air, spray with 2 percent 2,6-dichlorophenol-indophenol sodium in dehydrated *ethanol*, 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

TLC, using the plate coated with *silica gel GF254*

Mobile phase A: *Hexane*

Mobile phase B: A mixture of 95 volumes of *dichloromethane* and 5 volumes of *methanol.*

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

After each development, dry the plate in air and Examine by spray with 40 percent *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 (Rf 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.3 Migration of Elements / impurities

B.3.1. Extractable Metals (IP 2022/USP 661.1)

Zinc- 0.4 ppm
Chromium- NMT 0.02 ppm
Aluminium- 0.4 ppm
Titanium- 0.4 ppm
Zirconium- 0.04 ppm
Vanadium- 0.04 ppm
(Arsenic, Cadmium, Lead, Mercury, Nickel, Cobalt- NMT 0.01ppm)

***Preparation of Solution S3 (Acid extraction)*:** Place 5.0 g of the test material in a borosilicate glass flask with a round glass neck. Add 100 mL of 0.1 N hydrochloric acid and boil under a reflux condenser for 1 h with constant stirring. Allow to cool, decant the solution into a 250-mL volumetric flask, and dilute with 0.1 N hydrochloric acid to volume; the diluted solution is designated *Solution S3*.

Solution S3 is used for acid extractable metals.

Procedure for extract analysis: Instrumentation and methods (AAS/ICP-MS)

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

B.3.2. Overall migration (Optional test) NMT 60mg/kg or 10 mg/dm^2 (IS 9845) Selection of simulant and condition should be based on the type of product/ formulation. For the determination of specific and/or overall migration of constituents of plastics materials, IS 9845 shall apply.

B.3.3. Phthalic acid: (FSS-2018-2nd amend)/(Optional test)**:** It shall be done as prescribed in IS 3025-Methods Of Sampling And Test (Physical And Chemical) for Water and Wastewater.

B.3.4. Non-volatile residue (NVR) USP 661: This test quantifies any substances in the extract which do not volatilize at or above a temperature of 105°C.

Extracting medium: Unless otherwise directed in a specific test below, use Purified Water as the Extracting medium, maintained at a temperature of 70° during the extraction of the Sample preparation.

Blank: Use Purified Water where a blank is specified in the tests that follow.

Apparatus: Use a water bath and the Extraction Containers; Classification of Plastics, Apparatus. Proceed as directed in the first paragraph of Classification of Plastics, Preparation of Apparatus.

Sample preparation: From a homogeneous plastic specimen, use a portion, for each 20.0 mL of Extracting medium, equivalent to 120 cm^2 total surface area (both sides combined), and subdivide into strips approximately 3 mm in width and as near to 5 cm in length as is practical. Transfer the subdivided sample to a glass-stoppered, 250-mL graduated cylinder of Type I glass, and add about 150 mL of Purified Water. Agitate for about 30 s, drain off and discard the liquid, and repeat with a second washing.

Sample preparation extract: Transfer the prepared Sample preparation to a suitable extraction flask and add the required amount of Extracting medium. Extract by heating in a water bath at the temperature specified for the 24 h. Cool, but not below 20°. Pipet 20 mL of the prepared extract into a suitable container. *[Note—Use this portion in the test for Buffering Capacity.] Immediately decant the remaining extract into a suitably cleansed container, and seal.]*

Procedure: Transfer, in suitable portions, 50.0 mL of the Sample preparation extract to a suitable, tared crucible (preferably a fused-silica crucible that has been acid-cleaned) and evaporate the volatile matter on a steam bath. Similarly evaporate 50.0 mL of the Blank in a second crucible. [Note—If an oily residue is expected, inspect the crucible repeatedly during the evaporation and drying period, and reduce the amount of heat if the oil tends to creep along the walls of the crucible.]

Dry at 105° for 1 h: the difference between the amounts obtained from the *Sample preparation extract* and the *Blank* is NMT 15 mg.

Extracting medium for HDPE: Proceed the test as above, except that the *Blank* shall be the same solvent used in each of the following test conditions: the difference between the amounts obtained from the *Sample preparation* and the *Blank* is NMT 12.0 mg when water maintained at a temperature of 70° is used as the *Extracting medium*; is NMT 75.0 mg when alcohol maintained at a temperature of 70° is used as the *Extracting medium*; and is NMT 100.0 mg when hexanes maintained at a temperature of 50° is used as the *Extracting medium*.

Extracting medium for LDPE: Proceed the as above, except that the *Blank* shall be the same solvent used in each of the following test conditions: the difference between the amounts obtained from the Sample preparation and the Blank is NMT 12.0 mg when water maintained at a temperature of 70° is used as the Extracting medium; is NMT 75.0 mg when alcohol maintained at a temperature of 70° is used as the Extracting medium; and is NMT 350.0 mg when hexanes maintained at a temperature of 50° is used as the Extracting medium.

B.3.5. Buffering capacity*:* This test measures the amount of acid or base that is added to the extract which causes a significant change in ion activity (pH).

Titrate the previously collected 20 mL portion of the *Sample preparation extract (prepared in Non-volatile residue-B.3.4)* potentiometrically to a pH of 7.0, using either 0.010 N hydrochloric acid or 0.010 N sodium hydroxide, as required. Treat a 20.0-mL portion of the *Blank* similarly: if the same titrant was required for both the *Sample preparation extract* and the *Blank*, the difference between the two volumes is NMT 10.0 mL; and if acid was required for either the *Sample preparation extract* or the *Blank* and alkali for the other, the total of the two volumes required is 10.0 ml.

C. Functionality test:Spectral transmission (if Light protection is necessary) - (USP 661 -*Not official before 2025*)

Apparatus*:* If the suitability of the packaging system is demonstrated through stability testing, spectral transmission testing is not required, otherwise use a UV-visible spectrophotometer of suitable sensitivity and accuracy, adapted for measuring the amount of light transmitted by plastic materials used for pharmaceutical containers.

Procedure

Select a section to represent the average wall thickness. Cut a circular section from the packaging component or system, and trim as necessary to get a segment convenient for mounting in the spectrophotometer. After cutting, wash and dry the specimen, taking care to avoid scratching the surfaces. If the specimen is too small to cover the opening in the specimen holder, mask the uncovered portion of the opening with opaque paper or masking tape, provided that the length of

the specimen is greater than that of the slit in the spectrophotometer. Immediately before mounting in the specimen holder, wipe the specimen with lens tissue. Mount the specimen with the aid of a tacky wax, or by other convenient means, taking care to avoid leaving fingerprints or other marks on the surfaces through which light must pass. Place the section in the spectrophotometer with its cylindrical axis parallel to the plane of the slit and approximately cantered with respect to the slit. When properly placed, the light beam is normal to the surface of the section, and reflection losses are at a minimum.

Continuously measure the transmittance of the section with reference to air in the spectral region of interest with a recording instrument or at intervals of about 20 nm with a manual instrument, in the region of 290–450 nm.

Acceptance Criteria:

The observed spectral transmission is NMT the limits given in *Table 2* for plastic packaging components and systems intended for parenteral use. The observed spectral transmission for plastic containers for products intended for oral or topical administration does not exceed 10% at any wavelength in the range of 290–450 nm.

Spectral Transmission Limits for Plastic Packaging Components or Systems

Table 2

Nominal Size (mL)	Maximum Percentage of Spectral Transmission at Any Wavelength between 290 and 450 nm (%)
1	**25**
2	**20**
5	**15**

Table 3

Nominal Size (mL)	Maximum Percentage of Spectral Transmission at Any Wavelength between 290 and 450 nm (%)
10	**13**
20	**12**
50	**10**
>50	**10**

(Note—For components or systems of an intermediate size, the acceptance criterion is the spectral transmission of the next larger size)

5.2 POLYETHYLENE TEREPHTHALATE (PET) CONTAINERS/ CLOSURES

A. Identification of type of PET (by IR/ Differential scanning/UV IP-2022)

Test 1 -By FTIR Spectrometry

Dissolve 50 mg of the PET container specimen under examination in 2 ml of solvent blend of phenol and tetrachlorethane (60:40 w/w) with heating followed by centrifuging or 1,1,1,3,3,3 hexafluoropropan-2 or other appropriate solvent systems. Apply several drops of this solution on a glass plate. Keep this place 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 100-105^0 for about 1 hour)

Examine the film by infrared absorption spectrophotometry. The spectrum should show absorption maxima substantially at about 3053 cm2, 1955 cm1, 1725 cm1, 1613 cm1, 1455 cm, 1410 cm, 1265 cm1, 1020cm1, 973 cm1, 875 cm1, and 730cm1.

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 1000.0 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, the absorption maximum should be at about 240 nm.

Test 3 – By Differential Scanning Colorimetry

Conduct the entire test under nitrogen. Heat the specimen from room temperature to 290^0 at a heating rate between 10 and 20 per minute and hold it for 1 minute. Cool the specimen to room temperature at the highest cooling rate possible (typically, lower than a rate of 50^0 per minute) and hold it for 1 minute. Reheat it to 290^0 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 8.0^0.

B. Chemical test

B.1. Physicochemical test (Ref. IP-2022/ USP 661.1)

Tests using special solutions: Preparation of Special Solutions for Subsequent Tests on PET

Select required quantity of unlabeled, unmarked, and non-laminated portions from suitable containers, taken at random. Cut them in to pieces each having an area not more than 1cm^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 50^0 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 %) and reflux at 50^0 for 5 hours. Allow to cool and decant the solution.
Note: Use solution S2 within 4 hours of its preparation

Tests using the Special Solution (IP 2022)

B.1.1 Appearance: Solution S1 has to be clear

B.1.2. Absorbance of solution S1:
In the UV range (220nm to 340nm): 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.
B.1.3. Absorbance of solution S2:
In the visible range (400 nm to 800 nm): absorbance should be not more than 0.05.
B.1.4. Acidity: To 50.0 ml of solution S1 add 0.15 ml of BRP indicator solution. The solution turns yellow. Not more than 0.5ml of 0.01 M sodium hydroxide is required to change the color of the indicator to blue.
B.1.5. Alkalinity: To 50.0 ml of solution S1 and 0.2 ml of methyl orange solution. The solution turns yellow.
Not more than 0.5 ml of 0.01 M hydrochloric acid is required to reach the beginning of the colour change of the indicator to reach the beginning of the colour change of the indicator to orange.
B.1.6. Reducing substances (IP 2022): To 20.0 ml of solution S1, and 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 0.5ml.

B.2. Migration of Elements / Impurities

B.2.1. Extractable Metals (IP 2022)

Table 4
Extractable metals (using atomic absorption spectrometry)

As per IP2022	As per USP-661.1 & 661.2
Barium – NMT 1PPM Manganese -NMT 1PPM Zinc -NMT 1PPM Antimony -NMT 1PPM Titanium -NMT 1PPM Aluminium-NMT 1PPM Cobalt -NMT 1PPM	Barium-NMT 0.4 PPM Manganese -NMT 0.4 PPM Zinc -NMT 0.4 PPM Antimony-NMT 0.4 PPM Titanium -NMT 0.4 PPM Aluminium -NMT 0.4 PPM Germanium- NMT 0.4PPM (Arsenic, cadmium, lead, mercury, Nickel, Cobalt, Vanadium– NMT 0.01ppm)

Methodology: IP 2022
Test solutions:

Solution S3 (Acid Extraction): Place 20 g (Cut pieces having an area not more than $1cm^2$) of the sample into a round bottom flask. Add 50.0 ml of 0.1 M Hydrochloric acid and heat at 50^0 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 50^0 for 5 hours. Allow to cool and decant.
Use solution S4 within 4 hours of its preparation.

Extractable metals Tests using the Solution S3

- **Aluminium:** Not more than 1 ppm.
  Reference solutions. Prepare the suitably diluted solutions from reference standard solutions of aluminium (200 ppm A1) 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.

- **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.

- **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.

- **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.

- **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.

- **Zinc:** Not more than 1ppm
  Reference solutions. Prepare the 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.

Extractable metal Tests using the Solution S4

- **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.

B.2.2 Overall migration (Optional test) NMT 60mg/kg or 10 mg/dm^2: Selection of simulant and condition should be based on the type of product/ formulation. For the determination of specific and/or overall migration of constituents of plastics materials, IS 9845 shall apply.

B.2.3. Phthalic acid: (FSS-2018-2nd amend)/(Optional test)**:** It shall be done as prescribed in IS 3025-Methods Of Sampling And Test (Physical And Chemical) for Water and Wastewater.

B.2.4. Colorant Extraction (USP 661): Select 3 test bottles. Cut a relatively flat portion from the side wall of 1 bottle, and trim it as necessary to fit the sample holder of the spectrophotometer. Obtain the visible spectrum of the side wall by scanning the portion of the visible spectrum from 350 to 700 nm. Determine, to the nearest 2 nm, the wavelength of maximum absorbance. Fill the remaining 2 test bottles, using 50% alcohol for PET bottles and 25% alcohol for PETG bottles. Fit the bottles with impervious seals, such as aluminium foil, and apply closures. Fill a glass bottle having the same capacity as that of the test bottles with the corresponding solvent, fit the bottle with an impervious seal, such as aluminum foil, and apply a closure. Incubate the test bottles and the glass bottle at 49° for 10 days. Remove the bottles and allow them to equilibrate to room temperature. Concomitantly determine the absorbances of the test solutions in 5-cm cells at the wavelength of maximum absorbance, using the corresponding solvent from the glass bottle as the blank. The absorbance values so obtained are less than 0.01 for both test solutions.

B.3. Related Substances (Residual Monomers / Residual Inoroganics) -(IP2022/ USP 661):

B.3.1. Substances soluble in dioxane:

Place 2.0 g of the material to be examined in a round bottom flask. Add 20.0ml 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 Deg.
The residue weighs a maximum of 30.0 mg.

B.3.2. Sulphated ash: Not more than 0.5 per cent determined on 1.0g.

B.3.3. Total Terephthaloyl moieties. Not more than 1 ppm

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

For each extracting media fill enough test containers to 90 percent 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 49^0 for 10 days. Remove the test systems and glass bottles and store at room temperature. Do not transfer the extracting medium samples to alternative storage vessel.

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

Determine the absorbance of n-heptane extract at the wavelength of maximum absorbance at about 240nm. 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.

B.3.4. Ethylene glycol. Not more than 1 ppm.

Periodic acid solution. Dissolve 125 mg of periodic acid in 10.0 ml 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 and mix. Add 0.1 ml of disodium chromotropate solution to each flask and mix.

[Note–All the solutions should be analyzed 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, 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.

C. Functionality test: Spectral transmission (if Light protection is necessary) – Refer to test for Polyethylene 5.1 (C) Functionality Test.

5.3 POLYPROPYLENE CONTAINERS (PP) CONTAINERS/ CLOSURES

A. Identification Test

Test 1 - By FTIR Spectrophotometry

Apparatus: Use an infrared spectrophotometer capable of correcting for the blank spectrum and able to measure in transmission mode or equipped with an internal reflectance accessory and an appropriate internal reflectance plate.

Sample preparation

Transmission mode: Prepare a specimen of appropriate thickness (about 100 μm) without visible defects (cracks or holes). The specimens can be compressed to form a thin, uniform film by exposure to elevated temperatures and pressures (2000 psi or more). The temperatures at which the thin films are generated represent a trade-off between producing a melt (which dictates the lowest temperature necessary) and degrading the sample (which dictates the highest temperature allowed). Ultimately, the temperatures that are used are appropriate if the film produced is conducive to the infrared analysis.

Internal reflectance mode: Prepare a flat section and trim it as necessary to obtain a segment that is convenient for mounting in the internal reflectance accessory. Taking care to avoid scratching the surfaces, wipe the specimen with dry paper or, if necessary, a soft cloth dampened with methanol, and permits the surfaces to dry. Then securely mount the specimen on the internal reflection plate, ensuring adequate surface contact.

Procedure: Place the mounted specimen sections in the sample compartment of the infrared spectrophotometer or the internal reflectance accessory and place the assembly in the specimen beam of the infrared spectrophotometer. For internal reflectance, adjust the specimen position and mirrors within the accessory to permit maximum light transmission of the unattenuated reference beam. (For a double-beam instrument, attenuate the reference beam after completing the adjustment in the accessory to permit full-scale deflection during the scanning of the specimen.)

Determine the infrared spectrum from 3800 cm−1 to 650 cm−1 (2.6–15 μm).

Acceptance criteria: The specimen exhibits an absorption spectrum that is substantially equivalent to that of the USP 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 and RS spectra can be explained in the context of such natural compositional and/or physical variations.

Test 2 - By Differential Scanning Calorimetry

Sample preparation: Place an appropriately sized sample in the test specimen pan.

[Note—Intimate contact between the pan and the thermocouple is essential for obtaining reproducible results.]

Procedure: Determine the thermal analysis curve under nitrogen, using heating/cooling conditions specified for the polymer type and using equipment capable of performing the determinations as described in <891>. Heat the specimen from ambient to 30° above the melting point. Maintain the temperature for 10 min, and then cool to 50° below the peak crystallization temperature at a rate of 10°–20°/min.

Acceptance criteria: The melting peak temperature in the thermal analysis curve does not differ from that of USP Homopolymer Polypropylene RS by more than 12.0°.

B. Chemical test

B.1 Physicochemical Test: 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 round-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 SI 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 round-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 round-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 100ml volumetric flask, and dilute to volume with *0.1 M hydrochloric acid;* the diluted solution is *Solution S3*

Tests Using Special Solutions

B. l.1 Absorbance (IP 2022)

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

Absorbance should be not more than 0.2.

B.1.2. Acidity or alkalinity (IP 2022)

To 100.0 ml of Solution SI 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 S1, 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 M sodium hydroxide* is required to change the colour of the indicator to blue.

Not more than l .0 ml of *0.01M hydrochloric acid* is required to reach the beginning of the colour change of the indicator from yellow to orange.

B.1.3. Total organic carbon (IP 2022)

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.2 Migration Test

B.2.1 Extractable Metals (IP 2022)

Solution S3 is used for acid extractable metals.

Procedure for extract analysis:

Instrumentation and methods are those specified in Elemental Impurities (2.3.13 A –IP 2022)

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.

B.2.2. Overall migration- (Optional test) NMT 60mg/kg or 10 mg/dm^2: Selection of simulant and condition should be based on the type of product/ formulation. For the determination of specific and/or overall migration of constituents of plastics materials, IS 9845 shall apply.

B.2.3. Phthalic acid (FSS-2018-2nd amend)/(Optional test)**:** It shall be done as prescribed in IS 3025-Methods Of Sampling And Test (Physical And Chemical) for Water and Wastewater.

B.2.4. Colorant Extraction (USP 661): Select 3 test bottles. Cut a relatively flat portion from the side wall of 1 bottle, and trim it as necessary to fit the sample holder of the spectrophotometer. Obtain the visible spectrum of the side wall by scanning the portion of the visible spectrum from 350 to 700 nm. Determine, to the nearest 2 nm, the wavelength of maximum absorbance. Fill the remaining 2 test bottles, using 50% alcohol for PET bottles and 25% alcohol for PETG bottles. Fit the bottles with impervious seals, such as aluminium foil, and apply closures. Fill a glass bottle having the same capacity as that of the test bottles with the corresponding solvent, fit the bottle with an impervious seal, such as aluminum foil, and apply a closure. Incubate the test bottles and the

glass bottle at 49° for 10 days. Remove the bottles and allow them to equilibrate to room temperature. Concomitantly determine the absorbance of the test solutions in 5-cm cells at the wavelength of maximum absorbance, using the corresponding solvent from the glass bottle as the blank. The absorbance values so obtained are less than 0.01 for both test solutions.

B.2.5. Non-volatile residue (USP 661)

B.3. Polymer Additives (IP 2022)

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 (IP 2022)

Solvent mixture. 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 dichloromethane. 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 solution containing 0.01 per cent w/v of *butylated hydroxytoluene IPRS* and 0.024 per cent w/v of *polymer additive 01 IPRS* in the solvent mixture.

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

Reference solution (c). A solution containing 0.024 per cent w/v, each of, *polymer additive 04 IPRS* and *polymer additive 05 IPRS* in *dichloromethane.*

Reference solution (d). A 0.01 per cent w/v solution of *butylated hydroxytoluene IPRS* in the solvent mixture.

Reference solution (e). A 0.024 per cent w/v solution of *polymer additive 01 IPRS* in the solvent mixture.

Reference solution (f). A 0.024 per cent w/v solution of *polymer additive 06 IPRS* in the solvent mixture.

Reference solution (g). A 0.024 per cent w/v solution of *polymer additive 02 IPRS* in the solvent mixture

Reference solution (h). A 0.024 per cent w/v solution of *polymer additive 03 IPRS* in the solvent mixture.

Reference solution (i). A 0.024 per cent w/v solution of *polymer additive 04 IPRS* in *dichloromethane.*

Reference solution (j). A 0.024 per cent w/v solution of *polymer additive 05 IPRS* in *dichloromethane.*

Test A

Determine by liquid chromatography:

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

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

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-(l,ldimethylethyl)- 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 tertbutyl- 4-hydroxyphenyl)propionate; 2,2,23,6,6,63 -hexa-tertbutyl-4,4,43 -[(2,4,6-trimethyl-l,3,5-benzene-triyl) trismethylene] triphenol; octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl) prcpi<mate; tris(2,4-di-tert-butylphenyl) phosphate; 1,3,5-tris(3,5-di-tert-butyl-4-hydroxybenzyl)-s-triazine-2,4,6(l/7,377,5/7)-trione

Determine by liquid chromatography:

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 pm),
- mobile phase: a mixture of 60 volumes of *acetonitrile,* 30 volumes of *tetrahydrofuran* and 10 volumes of *water,*
- flow rate: 1.5 ml per minute,
- spectrophotometer set at 280 nm,
- injection-volume: 20 pl.

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to additive pentaerythrityltetrakis [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-l,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 modification

-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-buty|-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, using the plate coated with silica gel GF254.

Mobile phase A Hexane.
Mobile phase B Dichloromethane.

Dichloromethane, acidified. To 100.0 ml of dichloromethane, 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 dichloromethane acidified.

Reference solution (m). A 0.6 per cent w/v solution of polymer additive 08 IPRS in dichloromethane. Dilute 2.0 ml of the solution with dichloromethane, acidified to 10.0 ml.

Reference solution (n). A 0.6 per cent w/v solution of polymer additive 09 IPRS in dichloromethane. Dilute 2.0 ml of the solution with dichloromethane, acidified to 10.0 ml.

Reference solution (o). A 0.6 per cent w/v solution of polymer additive 10 IPRS in dichloromethane. Dilute 2.0 ml of the solution with dichloromethane, acidified to 10.0 ml.

Reference solution (p). A solution containing 0.6 per cent w/v, each of, polymer additive 10 IPRS and polymer additive 09 IPRS in dichloromethane. Dilute 2.0 ml of the solution with dichloro-methane, acidified to 10.0 ml.

Apply to the plate 20microlitre 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 mm. 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 w/v solution of stearic acid IPRS in dichloromethane.

Reference solution (s). A 0.2 per cent w/v solution of polymer additive 12 IPRS in dichloromethane.

Reference solution (t) A 0.2 per cent w/v solution of polymer additive 13 IPRS in dichloromethane.

Test A

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

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

Apply to the plate 10 microlitre 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, using the plate coated with silica gel GF254.

Mobile phase A. Hexane.
Mobile phase B. A mixture of 95 volumes of dichloromethane and 5 volumes of methanol.

Apply to the plate 10microlitre of sample solution S2C, reference solution (s) and reference solution (t). Develop the plates over a path of 13 cm with Mobile phase A and over 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).

C. Functionality test: Spectral transmission (if Light protection is necessary) – Refer to test for Polyethylene 5.1 (C) Functionality Test.

5.4 PHYSICAL TESTS:

For this purpose test prescribed in IS 2798-Methods of Test for Plastics Containers, shall apply.

6. Requirements for Eco Mark:

6.1 Product shall be eco marked with reference to the IS 8688.

6.2 For recycling of Plastic, IS: 14534- Plastics Recovery and Recycling of Plastics Waste — Guidelines shall apply.

7. SAMPLING

7.1 Sampling to be done as per method prescribed in IS 4905, Methods for Random Sampling.

8. PACKING AND MARKING

8.1 The containers shall be packed as agreed to between the purchaser and the supplier. Additionally, it is crucial to ensure that the bottles remain protected from external contaminants during both transport and storage.

8.2 The Phials/Droppers/Stoppers/Caps shall be packed by using Thermoform or Automatic packaging machine after sterilizing in sterilization plant using Ethylene oxide or Gamma radiations.

8.3 Each container, except in case of very small size, shall be permanently and legibly marked on its bottom with the manufacturer's name or registered trademark, if any.

BIS Certification Marking: The product may also be marked with Standard Mark.

The use of the Standard Mark is governed by the provisions of the Bureau of Indian Standards Act, 1986 and the Rules and Regulations made thereunder. The details of conditions under which the license for the use of Standard Mark may be granted to manufacturers or producers may be obtained from the Bureau of Indian Standards.