Doc. No: PCD 21 (21332) WC
December 2022

BUREAU OF INDIAN STANDARDS
DRAFT FOR COMMENTS ONLY

Draft Indian Standard

PLASTIC CONTAINERS FOR PHARMACEUTICAL USE — SPECIFICATION

PART 2 PARENTERAL AND OPHTHALMIC PREPARATIONS

(*First Revision* of IS 7803 (Part 2))

(ICS 83.080.01)

Plastics packaging Sectional Committee, PCD 21

Last date for receipt of comment is **31 January 2023**

FOREWORD

(Formal clause will be added later**)**

This Indian Standard was originally published in 1975. This revision has been undertaken to update the cross-referred standards and incorporate the amendment.

With the growth of indigenous plastics packaging industry, plastic containers arc replacing conventional containers made of materials, such as glass and metal. Plastic containers are also being increasingly used for pharmaceutical trade.

The package requirements for pharmaceutical preparations can broadly be classified into the following two categories, depending upon their use and requirements:

a) Parenteral and ophthalmic preparations; and
b) Other than parenteral and ophthalmic preparations.

Since the containers for parenteral and ophthalmic preparations have to meet additional requirements, it was felt necessary to cover the containers for different purposes in separate parts of this standard. Part 1 of this standard covers containers for preparations other than parenteral and ophthalmic while this part covers those for parenteral and ophthalmic preparations.

A scheme of labelling environment friendly products with the ECO logo has been introduced at the instance of the Ministry of Environment and Forests (MEF), Government of India. The ECO-Mark is being administered by the Bureau of Indian Standards (BIS) under the BIS Act, 1986 as per the Resolutions No. 71 dated 21 February 1991 and No. 425 dated 28 October 1992 published in the Gazette of the Government of India. For a product to be eligible for marking with the ECO logo, it shall also carry the ISI Mark of the BIS besides meeting additional environment friendly

requirements. For this purpose, the Standard Mark would be a single mark being a combination of the ISI Mark and the ECO logo.

For the purpose of deciding whether a particular requirement of this standard is complied with, the final value, observed or calculated, expressing the result of a test or analysis, shall be rounded off in accordance with IS 2 :2022 'Rules for rounding off numerical values (*second revision*)'. The number of significant places retained in the rounded off value should be the same as that of the specified value in this standard.

1 SCOPE

This standard (Part 2) prescribes requirements for plastic containers for parenteral and ophthalmic preparations.

2 REFERENCE

The following standards contain provisions which through reference in this text constitute provisions of this standard. At the time of publication the editions indicated were valid. All standards are subject to revisions, and parties to agreements based on this standard are encouraged to investigate the possibility of applying the most recent editions of the standard indicated below.

IS No.	***Title***
IS 7019 : 1998	Glossary of terms in plastics and flexible packaging, excluding paper (*second revision*)
IS 9833 : 2018	List of colourants for use in plastics in contact with foodstuffs and pharmaceuticals (*second revision*)
PCD 12 (21330)	Polyethylene containers for pharmaceutical use — Specification : Part 1 Other than parenteral and ophthalmic preparations (*second revision* of IS 7803 (Part 1))

3 TERMINOLOGY

3.1 For the purpose of this standard, definitions given in IS 7019 shall apply.

4 REQUIREMENTS

4.1 Material — Only virgin plastic material, which is practically odourless, shall be used in the manufacture of the containers or any accessory product. Pigments used, if any, shall conform to IS 9833.

4.2 Transparency — The container shall be sufficiently transparent for the contents to be adequately inspected.

4.3 Sterilizability — A filled container shall be sterilizable by heat or any other acceptable method without showing signs of shrinkage, distortion, discoloration, loss of transparency, cracking, tackiness, or other deterioration.

4.4 Size and Design — The size, shape and design of the container shall be as agreed to between the purchaser and the vendor.

5 PERFORMANCE TESTS

5.1 The container shall be subjected to the fol1owing tests to be performed in accordance with the methods prescribed in IS 7803 (Part 1).

a) Leakage test; and
b) Collapsibility test.

5.2 Container Material Tests

5.2.1 The material of the container shall be subjected to the following tests to be performed in accordance with the methods prescribed in IS 7803 (Part 1).

a) Clarity of aqueous extract;
b) Water soluble impurities content;
c) Non-volatile residue of aqueous extract; and
d) *p*H value.

5.2.2 *Toxicological Test* — The material shall pass the following tests when tested in accordance with the method prescribed in Annex mentioned against each.

a) Systemic injection test (Annex A);
b) Intracutaneous test (Annex B); and
c) Implantation test (Annex C).

5.2.3 *Freedom from Foaming* — The material when tested in accordance with tbc method prescribed in Annex D shall pass the test.

6 ADDITIONAL REQUIREMENTS FOR ECO-MARK

6.1 General Requirements

6.1.1 The product shall conform to the requirements for quality, safety and performance prescribed.

6.1.2 The manufacturer shall produce to BIS the consent clearance as per the provisions of *Water Prevention and Control of Pollution Act*, 1974 and *Air Prevention and Control of Pollution Act*, 1981 along with the authorization, if required under *Environment Protection Act*, 1986 and the Rules made thereunder while applying for the ECO-Mark. The manufacturer shall produce documentary evidence with respect to the compliance of regulation under *Prevention of Food Adulteration Act*, 1954 and *Drugs and Cosmetic Act*, 1940 and Rules made thereunder, wherever necessary.

6.1.3 The product must display a list of critical ingredients in descending order of quantity present expressed as percent of the total. The list of such ingredients shall be identified by Bureau of Indian Standards.

6.1.4 The product packaging shall display in brief the criteria based on which the product has been labelled as 'Environment Friendly'.

6.1.5 The material used for product packaging shall be recyclable or biodegradable.

6.1.6 It shall also suitably mention that ECO-Mark label is applicable only to the packaging material/package, if content is not separately covered under ECO-Mark. It may be stated that ECO-Mark is applicable to the product or packaging material or both.

6.2 Product Specific Requirements

For the manufacture of this product one or more of the virgin material covered in following Indian Standard shall be used:

IS No.	*Title*
10142 : 1999	Polystyrene (crystal and high impact) for its safe use in contact with foodstuffs, pharmaceuticals and drinking water — Specification (*first revision*)
10146 : 1982	Specification for polyethylene for its safe use in contact with foodstuffs, pharmaceuticals and drinking water
10151 : 2019	Polyvinylchloride (PVC) and its copolymers for its safe use in contact with foodstuffs, pharmaceuticals and drinking water — Specification (*first revision*)
10910 : 1984	Specification for polypropylene and its copolymers for its safe use in contact with foodstuffs, pharmaceuticals and drinking water
11434: 1985	Specification for ionomers resins for its safe use in contact with foodstuffs, pharmaceuticals and drinking water
11704 : 1986	Specification for ethylene acrylic acid (EAA) copolymers for its safe use in contact with foodstuffs, pharmaceuticals and drinking water
12247 : 1988	Specification for Nylon-6 polymer for its safe use in contact with foodstuffs, pharmaceuticals and drinking water
12252 : 2017	Polyalkylene terephthalates (PET & PBT), their copolymers and list of constituents in raw materials and end products for their safe use in contact with foodstuffs and pharmaceuticals (*first revision*)

7 PACKING AND MARKING

7.1 The packing and marking of the containers shall be as prescribed in IS 7803 (Part 1).

8 SAMPLING AND CRITERIA FOR CONFORMITY

8.1 The sampling procedure and criteria for conformity shall be as prescribed in IS 7803 (Part 1).

ANNEX A
(*Clause* 5.2.2(a))

SYSTEMIC INJECTION TEST

A.1 TEST ANIMALS

A-1.1 Select healthy adult mice not previously used for any test, each weighing between 17 and 23 g. For each test group, use only mice of the same source. Offer food and water ad libitum.

A-2 APPARATUS

A-2.1 The apparatus for the tests shall include the following:

A-2.1.1 *Autoclave* — Capable of maintaining a temperature of 121 ± 5 °C, equipped with a thermometer, a pressure gauge, a vent cock, a rack adequate to accommodate the test containers above the water level, and a water cooling system that will allow cooling for the test container to about, but not below 22 ºC immediately following the heating cycle.

A-2.1.2 *Oven* — Use an oven, preferably a forced-circulation model, that will maintain operating temperature of 50 °C or 70 ºC within ± l ºC.

A-2.1.3 *Extraction Containers* — Use containers, such as ampules or screw cap culture test tubes of borosilicate glass. If used culture test tubes are closed with screw caps having suitable rubber liners, the exposed surface of the rubber liner should be completely protected with an insert solid disk 0.050 to 0·075 mm in thickness. A suitable disk may be fabricated from a polytetrafluoroethylene resin.

A-2.2 Preparation of Apparatus — Clean all glassware thoroughly with chromic acid cleansing mixture or if necessary with hot nitric acid, followed by prolonged rinsing with water. Clean cutting devices by an appropriate method (for example, successive cleaning with acetone and methylene chloride) prior to use in subdividing a specimen. Clean all other equipment by thoroughly scrubbing with a suitable detergent and prolonged rinsing with water.

A.2.2.1 Render containers and devices used for extraction and in transfer and administration of test material, sterilize and dry by a suitable process.

NOTE — If ethylene oxide is used as the sterilizing agent, allow adequate time for complete de-gassing.

A-3 EXTRACTING MEDIA

A-3.1 The extracting media to be used for the test shall include the following:

a) *Sodium Chloride Injection* — A sterile and pyrogen-free solution of sodium chloride in water for injection. It contains 0·9 percent of sodium chloride;
b) *1 in 20 Solution of Alcohol* in *Sodium Chloride Injection;*
c) *Polyethylene Glycol 400;* and
d) *Vegetable Oil* — Use freshly refined sesame oil or cottonseed oil or arachis oil that meets the following additional requirement:

Using three test animals prepared as directed under test animals for Intracutaneous test (*see* Annex B), inject 0.2 ml intracutaneously at each of 10 sites on each animal and examine the injected sites 24, 48 and 72 h after the injections. No site should show a greater reaction than oedema or erythema over an area 0.5 cm in diameter.

A-4 PREPARATION OF SAMPLES

A-4.1 Unless otherwise stated, use only borosilicate glassware, analytical grade reagents, and double distilled water from an all-glass distilling apparatus.

A-4.2 Select and subdivide into portions a sample of the size indicated in Table 1, place the portions from each sample in an extraction container, and clean them by shaking for about 30 s with two 70 ml portions of water for injections discarding the waste water each time. Allow the portions to drain dry and in addition, further dry those intended for extraction in vegetable oil by heating at 50 °C for 1 h.

NOTE — Do not clean with a dry or a wet cloth or any organic solvent, surfactant, etc.

Table 1 Surface Area of Sample to Be Used
(*Clause* A-4.2)

Form of Plastic	Class	Amount of Sample for Each 20 ml of Extracting Medium	Subdivision of Samples
(1)	(2)	(3)	(4)
Film or sheet	A	Equivalent of 120 cm^2 total surface area	Strips of about 5 × 0.3cm
	B	Equivalent of 60 cm^2 total surface area	
Tubing	A*	Length (in cm) = 120 cm^2/(Sum of I. D and O.D. circumferences)	Section of about 5 × 0.3cm
	B*	Length. (in cm) = 60 cm^2/(Sum of I. D. and O.D. circumferences)	
Slabs, tubing and moulded items	C	Equivalent of 60 cm^2 total surface area	Pieces up to about 5 × 0.3cm

NOTES:

1. Class A is < 0·5 mm in thickness; Class B is 0·5 to 1 mm in thickness; Class C is >1 mm in thickness.
2. * Wall thickness of tubing.

A-4.3 Add 20 ml portions of the appropriate extracting media to separate extraction containers. Add 1 portion of the sample to each of 2 containers of each set, leaving the contents of a third

container to serve as the blank. Close each container, and if the container is of screw cap type, seal the closure with pressure sensitive tape, and depending upon the kind of plastic concerned apply heat as follows:

a) In an oven at 50 °C for 72 h;
b) In an oven at 70 °C for 24 h; or
c) In an autoclave at 121 °C for 1 h.

A-4.4 The extraction should not result in gross physical changes in the samples, such as fusion of the two portions in any way beyond a slight adherence of one portion to another. Cool to about room temperature but not below 22 °C, shake vigorously and decant each extract, using asceptic precaution, into a dry, sterile vessel. Store the extracts at a temperature between 22 and 80 °C and do not use for tests after 24 h.

A-5 PROCEDURE

A-5.1 Inject each extract of the sample, and the corresponding blank into groups of 5 mice each in the amount and by the route given in Table 2. Observe the animals immediately after injection, again 4 h after injection, and then not earlier than 24, 48 and 72 h, after injection.

TABLE 2 Amounts and Routes of Systemic Injection of Extracts and Blanks
(*Clause* A-5. l)

Extract or Blank	Dose (Per Kg)	Injection	
		Route	Rate, ml/s
(1)	(2)	(3)	(4)
Sodium chloride injection 1 in 20 solution of alcohol in sodium chloride injection	50 ml 50 ml	i.v i.v	0.1 0.1
Polyethylene glycol 400	10 g	i.p	–
Vegetable oil	50 ml	i.p	–

A-6 Test Results

A-6.1 The sample shall pass the test if during the observation period none of the animals treated with the extract of the sample shows a significantly greater reaction than the animals treated with the blank.

A-6.2 If any animals treated with the sample show slight signs of toxicity, and not more than l animal shows symptoms of toxicity or dies, repeat the test using groups of 10 mice each. On the repeated test, the requirements of the test are met if none of the animals treated with the sample shows a significantly greater reaction than that observed in the animals treated with the blank.

ANNEX B

[*Clauses* 5.2.2(b) *and* A-3.1(d)]

INTRACUTANEOUS TEST

B-1 TEST ANIMALS

B-1.1 Select healthy, thin skinned albino rabbits not previously used for any test, whose fur can be clipped closely and whose skin is free from mechanical irritation or trauma. On the day of the test, clip the fur from the test area. Divide the latter into grid of suitably identified individual injection sites, 10 on each side of the spinal column.

NOTE — In handling the animals, avoid touching the injection sites during observation periods.

B-2 APPARATIIS

B-2.1 The apparatus shall be as prescribed in Annex A.

B-3 EXTRACTING MEDIA

B-3.1 The extracting media for the test shall be as prescribed in Annex A.

B-4 PREPARATION OF THE SAMPLES

B-4.1 The samples for the test shall be prepared in the same way as prescribed in Annex A.

B-5 PROCEDURE

B-5.1 Inject intracutaneously 0·2 ml of each extract of each sample at 10 sites on one side of each of 2 rabbits. Similarly, at 5 other sites on each rabbit, inject 0·2 ml of the corresponding blank. Examine the injected sites 24, 48 and 72 h after the injection for gross evidence of tissue reaction, such as erythema, oedema and necrosis. To facilitate the examination, swab the skin lightly with diluted alcohol. Rate the observations on a numerical scale that permits striking averages for the extract of the sample and for the blank, respectively.

NOTE — Dilute the extracts or the sample prepared with polyethylene glycol 400 and a corresponding blank, with 8·3 volumes of sodium chloride injection to obtain a concentration of 120 mg of polyethylene glycol per millilitre.

B-6 TEST RESULTS

B-6.1 The sample shall be deemed to have passed the test if during the observation period, the average for the extract of the sample is not significantly greater than that for the blank.

B-6.2 If the result is doubtful, repeat the test using fresh extracts in 3 more rabbits. The requirements of the test shall he met if on the repeated test the average for the extract of the sample is not significantly greater than that for the blank.

ANNEX C
[*Clause* 5.2.2(c)]

IMPLANTATION TEST

C-1 TEST ANIMALS

C-1.1 Select healthy adult rabbits, not previously used for any test, each weighing not less than 2 .5 kg and having well developed paravertebral muscles. The animals may be anesthetized suitably to prevent muscular movements, such as twitching, while the samples are being implanted. On the day of the test or up to 20 h before testing, clip the fur of the animals on both sides of the spinal column. Remove loose fur by means of vacuum.

C-2 PREPARATION OF SAMPLE

C-2.1 Prepare the sample for implantation by reducing it to strips about 1.0 mm wide and 10 mm long and by inserting the strips in 19 mm, 15 gauge intravenous needles.

NOTE — Use aseptic precautions if the strips and needles have been sterilized previously, otherwise suitably sterilize the combined strip and needle. If an agent, such as ethylene oxide, is used as the sterilizing agent, allow adequate time for complete de-gassing.

C-3 PROCEDURE

C-3.1 Into the paravertebral muscles of each of 2 rabbits prepared as directed in **C-1**, implant 4 strips of the sample and 2 strips of the corresponding negative control. Place the strips at intervals of about 2.5 cm on each side of and about 3.5 cm from the spinal column. In making an implant, insert the needle parallel with the spinal column, at an angle of 30° and then use a stylet to hold the strip in place as the needle is withdrawn. If excessive bleeding is observed after implantation of a strip, place a duplicate strip at another site.

C-3.2 Keep the animals for a period of not less than 72 h, and sacrifice them at the end of the observation period by administering an overdose of an anesthetic agent. Allow sufficient time to elapse for the tissue to be cut without bleeding. Examine macroscopically the area of the tissue surrounding the centre portion of each implant strip. Use a magnifying lens, if necessary. The tissue immediately surrounding the negative control strips, appears normal and entirely free from haemorrhage, film or encapsulation.

C-4 TEST RESULTS

C-4.1 The requirements of the test shall be met if in each rabbit the reaction to not more than 1 of the 4 sample strips is significantly greater than that to the negative control strips.

NOTE — Use negative control strips obtainable which come in strips 1 mm wide and 10 mm long.

ANNEX D
(*Clause* 5.2.3)

TEST FOR FREEDOM FROM FOAMING

D-1 APPARATUS

D-1.1 A large test-tube that has been cleaned with chromosulphuric acid and thoroughly rinsed with double distilled water.

D-2 PROCEDURE

D-2.1 Take at random about 10 pieces of the samples in accordance with a total surface area of about 50 cm^2 and rinse with double distilled water. Transfer these to the test-tube, add 10 ml of double distilled water, and shake vigorously for 3 min.

D-3 TEST RESULTS

D-3.1 The sample shall be deemed to have passed the test if any foam that is formed, disappears within 30 s after shaking has been stopped.