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Plastic containers for intravenous injections

Récipients en plastique pour injections intraveineuses

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

ISO 15747 was prepared by Technical Committee ISO/TC 76, *Transfusion, infusion and injection equipment for medical and pharmaceutical use*.

This second edition cancels and replaces the first edition (ISO 15747:2003), which has been technically revised. Especially Annex C was totally revised in order to refer to the International Standards of the ISO 10993 series, which specifies the biological assessment of medical products.

Introduction

In some countries, national or regional pharmacopoeias or other government regulations are legally binding and these requirements take precedence over this International Standard.

Plastic containers for intravenous injections

1 Scope

This International Standard contains requirements that relate to the safe handling and the physical, chemical and biological testing of plastic containers for parenterals.

This International Standard is applicable to plastic containers for parenterals having one or more chambers and having a total nominal capacity in the range of 50 ml to 5 000 ml such as film bags or blow-moulded plastic bottles for direct administration of infusion (injection) solutions.

2 Normative references

The following referenced documents are indispensable for the application of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 2859-1, *Sampling procedures for inspection by attributes — Part 1: Sampling schemes indexed by acceptance quality limit (AQL) for lot-by-lot inspection*

ISO 8536-4, *Infusion equipment for medical use — Part 4: Infusion sets for single use, gravity feed*

ISO 10993 (all parts), *Biological evaluation of medical devices*

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

3.1
access port
area of the infusion container consisting of the insertion point and the injection point, if applicable

3.2
cover
part that protects the access port during storage and also provides evidence that the infusion container has been tampered with

NOTE The cover can also envelop the entire container (e.g. outer bag).

3.3
empty container
raw container with identification, which is suitable for the acceptance, storage and administration of the injection solution

3.4
hanger
that part of the container that is used to hang it up

3.5
identification
paper or foil label or printing or embossing

3.6
infusion container
container filled to its nominal capacity with parenteral injection product and with identification for the storage and administration of the parenteral injection product

3.7
injection point
point for injecting pharmaceuticals

NOTE 1 The injection point and the insertion point can be identical.

NOTE 2 Some containers intentionally do not have an injection point.

3.8
insertion point
point which accepts the insertion part of the infusion device

3.9
nominal capacity
intended or declared fluid volume of a container

3.10
raw container
empty container that has not yet been sterilized and has no identification

3.11
sheeting
plastic film, foil or sheeting intended for the production of empty containers

4 Requirements

4.1 Physical requirements

4.1.1 Manufacturing process compatibility

The infusion container shall comply with the requirements given in 4.1.2 to 4.1.5 and 4.1.7 to 4.1.10 after the manufacturing process (such as sterilization).

4.1.2 Resistance to temperature, pressure and leakage

The infusion container shall withstand alternating thermal stress, shall be resistant to pressure and shall be leak-free when tested as specified in A.3.

4.1.3 Resistance to dropping

The infusion container shall sustain no damage after being dropped when tested as specified in A.4.

4.1.4 Transparency

The infusion container shall be sufficiently transparent so that suspended particles, turbidity and discoloration can be recognised when tested as specified in A.5. Alternative procedures may be used.

NOTE Blocking of UV radiation should be considered depending on the content of the container.

4.1.5 Water vapour permeability

Unless otherwise defined for specific applications or uses, the packed infusion container shall not lose more than 5 % of its mass during the period of usability, when tested as specified in A.6.

NOTE Permeability of other gases (e.g. oxygen) should be taken into account depending on the content of the container.

4.1.6 Particulate contamination

Infusion containers shall be manufactured so that contamination with particles is avoided.

When empty infusion containers are tested as specified in A.7, no more than 25 particles with a diameter $\geqslant$ 10 µm and no more than 3 particles with a diameter $\geqslant$ 25 µm shall be found per millilitre of nominal capacity. Finished parenteral solutions in the infusion containers shall comply with relevant pharmacopoeial requirements for finished product particulate matter.

4.1.7 Cover

The access port shall be protected by a cover. Its intactness is determined by visual inspection. It shall be possible to remove the cover without using mechanical aids.

4.1.8 Access port

It shall be possible to pierce the insertion point with the insertion part of an infusion device as specified in ISO 8536-4. The force shall not exceed 200 N at an insertion rate of 500 $mm \cdot min^{-1}$, when tested as specified in A.8.

4.1.9 Adhesion strength of the infusion device and impermeability of the insertion point

The material and design of the access port shall be suitable for accepting the insertion part of an infusion device in accordance with ISO 8536-4, for sealing off the insertion point and for holding the insertion part firmly when subject to tensile load. When tested as specified in A.9 no leakage shall occur and the insertion part shall not slide out from the insertion point. The removal force shall be greater than 15 N.

4.1.10 Injection point

If the container has an injection point, this shall not leak after puncturing and removal of the cannula when tested as specified in A.10.

4.1.11 Hanger

It shall be possible to hang the infusion container up when it is in use. The hanger shall withstand a tensile load when tested as specified in A.11.

4.1.12 Identification

The identification characters shall be clearly legible, and affixed labels shall not become detached when tested as specified in A.12.

4.2 Chemical requirements

4.2.1 Requirements for the raw container or the sheeting

The sheeting shall fulfil the requirements given in the relevant pharmacopoeias. Alternatively, it may be tested as described in Table 1.

Table 1 — Requirements for the raw container or the sheeting

Requirements	Maximum permissible value	Test as specified in
Residue on ignition:		B.2
polyolefins	5 mg/g	
polyvinyl chloride, containing plasticizers	1 mg/g	
Metals: Ba, Cd, Cr, Cu, Pb, Sn	for each metal, 3 mg/kg	B.3

4.2.2 Requirements for the test fluid

The test fluid shall be prepared as specified in B.4. No coloration, but weak opalescence of the test fluid, is permissible. It shall fulfil the requirements specified in Table 2.

Table 2 — Requirements for the test fluid

Requirements	Maximum permissible value	Test as specified in
Acidity or alkalinity	0,4 ml sodium hydroxide solution [c(NaOH) = 0,01 mol/l] 0,8 ml hydrochloric acid [c(HCl) = 0,01 mol/l]	B.6
UV absorbance	in the range of 230 nm to 360 nm: $\leqslant$ 0,25 for infusion containers with a nominal capacity $\leqslant$ 100 ml $\leqslant$ 0,2 for infusion containers with a nominal capacity > 100 ml	B.7
Evaporation residue	5 mg	B.8
Oxidizable constituents	1,5 ml	B.9
Ammonia	0,8 mg/l	B.10
Metals: Ba, Cr, Cu, Pb Sn, Cd Al	 for each metal, 1 mg/l for each metal, 0,1 mg/l 0,05 mg/l	B.11
Heavy metals	2 mg/l	B.12

4.3 Biological requirements

4.3.1 Impermeability for microorganisms

The infusion container shall be impermeable to microorganisms when tested as specified in C.2.

4.3.2 Migration/tolerance

The materials used for the manufacture of infusion containers (e.g. films, wrappings, adhesives, adhesion promoters, printing inks) shall not release into the infusion solution any substances in such quantities that they have a pyrogenic or toxic effect when tested as specified in C.3, C.4 and the ISO 10993 series.

5 Identification

Identification shall be in accordance with the relevant laws and specifications.

6 Application of tests

A distinction is made between type testing and batch testing. All tests specified in Annexes A to C are type testing. They shall be repeated if one or more of the following conditions is changed significantly so that the requirements as specified in Clause 4 might be affected:

— the design;

— the plastic composition;

— the process of manufacturing the infusion container;

— the sterilization process.

Annex A
(normative)

Physical tests

A.1 General

Physical testing shall be performed using an infusion container filled up to the nominal capacity with infusion solution or with water.

A.2 Sampling

Take samples required for the tests specified in A.3 to A.12 in accordance with the requirements of statistical quality control for sampling for the type test, e.g. according to ISO 2859-1.

A.3 Resistance to temperature stability, pressure and leakage

Store infusion containers for 24 h at (–25 ± 5) °C and subsequently for 24 h at (50 ± 5) °C, and then subject them to an internal pressure of 50 kPa between two plane parallel plates at (20 to 30) °C. Maintain this pressure for 15 min. An equivalent test method may be used in which an external pressure, such as a pressure cuff, is applied to the bag in order to generate an equivalent internal pressure.

The test is passed if no leakage can be determined on visual inspection. The test does not apply to the internal seals separating chambers within a container.

For infusion containers labelled “protect from freezing”, omit storage at –25 °C.

A.4 Resistance to dropping

Drop infusion containers on a hard, rigid, smooth surface at a temperature of (20 to 30) °C. Determine the height of drop in accordance with Table A.1, depending upon the nominal capacity of the infusion container.

The test is passed if no infusion container is broken and no leakage can be determined on visual inspection.

Table A.1

Nominal capacity ml	Height of drop m
50 to 749	1,00
750 to 1 499	0,75
1 500 to 2 499	0,50
2 500 and above	0,25

A.5 Transparency

Prepare a stem suspension as follows:

a) Dissolve 6,0 g hydrazine sulfate for analysis in 400 ml clear water.

b) Dissolve 60,0 g hexamethylenetetramine for analysis in 400 ml clear water.

c) The two solutions are poured consecutively into a 1 l measuring flask, filled to 1 l with clear water.

d) Leave the solution to stand for 48 h at (20 to 30) °C so that a formazine suspension can develop.

Dilute the stem suspension according to a) to d) 1:100. Fill an empty infusion container to nominal capacity with the diluted suspension, and fill an additional emptied infusion container with clear water. In the case of infusion containers which have been sterilized, allow them to remain undisturbed for 3 h prior to inspection.

The test is passed if, on visual inspection, the turbidity of the formazine suspension in comparison with water is clearly detectable against a black, dull-finished background. Conduct the inspection at an illumination intensity in the range (8 000 to 10 000) lx provided by incandescent light sources directly above and below the container, which illuminate the container at an angle of approximately 90° to the axis of observation. The light sources shall illuminate the infusion container directly, i.e. be shielded from the analyst's eyes.

Instead of the above-mentioned formazine suspension an equivalent standard and/or method may be used.

A.6 Water vapour permeability

Store infusion containers in final packaging at (20 to 30) °C, with a relative humidity of (40 ± 5) %, and without exposure to direct light.

Unless otherwise defined for specific applications or uses, the test is passed if the rate of decrease in mass for each individual infusion container does not exceed 5 % during the period of usability. Suitable methods for shortening the testing duration are permissible (e.g. accelerated testing as specified in ICH[1)] guidelines[1]).

A.7 Particulate contamination

Fill empty containers, under cleanroom conditions to the nominal capacity, with water for injection which has been filtered previously through a membrane filter with a pore size of 0,2 µm. Process the containers according to their intended use (filling, sterilization) and store for at least 12 h.

Then determine the particle content of the container's contents using a particle-counting device that functions according to the light blockage method. Take into account the values of the blank sample.

A.8 Penetration ability

Pierce the infusion containers at the insertion point with a test spike in accordance with ISO 8536-4.

1) ICH: International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

A.9 Adhesion strength of the infusion device and impermeability of the insertion point

After piercing the infusion containers as described in A.8, each test spike shall remain in the insertion point for 5 h. Then place the infusion containers between two plane parallel plates, loaded with an internal pressure of 20 kPa for 15 s, and inspect for any leakage. After completing the pressure test, measure the force needed for removal of each test spike from the insertion point at a speed of 100 $mm \cdot min^{-1}$.

If the infusion container is intended to be used with a pressure cuff, perform the test with an internal pressure of 50 kPa for 15 min.

A.10 Tightness of the injection point

Puncture the injection point of the container with a cannula having an outside diameter of 0,6 mm or 23 gauge. Keep the cannula in position for 15 s. After the cannula is removed, test the injection point in water subjected to a pressure of 20 kPa for 15 s. Examine the injection point for signs of air leakage.

A.11 Hanger

Hang up the infusion container (as defined in 3.6) using the hanger (as defined in 3.4), and then apply an additional tensile force of 15 N for 60 min.

A.12 Identification

Store the infusion containers completely submerged in water for 24 h at (20 to 30) °C. The characters shall remain clearly legible. Paper or foil labels shall not detach.

Annex B
(normative)

Chemical tests

B.1 General

Chemical tests apply to the empty container or the sheeting.

For all chemical tests specified, equivalent methods as described in pharmacopoeias may be used.

B.2 Determination of the residue on ignition

Weigh 1,00 g to 2,00 g of the container material (in small pieces) in a suitable crucible that has been previously ignited, cooled and weighed. Heat to (100 to 105) °C for 1 h. Then ignite to (550 ± 25) °C. Allow to cool in a desiccator and weigh. Repeat ignition until constant mass is attained. Calculate mass of residue on ignition per gram of starting material.

Equivalent methods as described in pharmacopoeias may be used.

B.3 Determination of metals in the plastic

Determine the metals present by atomic spectrometric analysis of a hydrochloric acid leach of the ignition residue.

Equivalent methods as described in pharmacopoeias may be used.

B.4 Preparation of the test fluid

Fill the empty container twice to the nominal capacity with water for injection, shake for approximately 1 min and then empty. After the rinse water has drained off, fill the empty container to the nominal capacity with water for injection. Then compress the container so that the remaining air escapes from the container, and subsequently close it. Extract the container for at least 30 min in pressurized, saturated steam at (121 ± 2) °C. Use 250 ml water for injection as a comparator fluid (blank sample). Heating-up and cooling times are not included in the 30 min cycle time requirement.

If appropriate, the extraction may be performed on pieces of sheeting or raw container. Use pieces with a total surface area of 1 500 cm^2. Wash this material twice with 100 ml water for injection and discard the water after use. Drain the pieces, cover them with 250 ml water for injection and extract for 30 min in pressurized, saturated steam at (121 ± 2) °C. As a comparison fluid (blank sample), treat water for injection in the same manner.

If the container is not intended for sterilization at temperatures of at least 121 °C, then the extraction may also be performed at (100 ± 2) °C for a duration of 2 h or at (70 ± 2) °C for a duration of (24 ± 2) h, in which case the selected temperature should not be lower than that at which the infusion container is used.

In the event that the solution resulting from extraction of a single container or single sample of sheeting has insufficient volume to allow for all of the required testing, the solutions from two or more extractions may be combined to produce a composite test solution. In case alternative sterilization methods other than thermal sterilization are to be applied to the container, e.g. γ-irradiation, ethylene oxide or e-beam, use sterilized containers for preparation of the test fluid.

B.5 Determination of turbidity and coloration

Determine turbidity and coloration by visual inspection. Appropriate procedures according to pharmacopoeias may be used.

B.6 Determination of acidity or alkalinity

After the addition of 2 drops of phenolphthalein solution, 10 ml of the test fluid shall show no red coloration. However, on the addition of less than 0,4 ml caustic soda [c(NaOH) = 0,01 mol/l], red coloration shall occur. After the addition of 0,8 ml hydrochloric acid [c(HCl) = 0,01 mol/l], this coloration shall disappear again. On the addition of 5 drops methyl red solution, the solution shall have an orange-red coloration.

B.7 Determination of the UV absorption

Determine photometrically the UV absorbance of the test fluid against the comparison fluid in a 1 cm cuvette.

B.8 Determination of the evaporation residue

Evaporate 100 ml of the test fluid on a water bath and dry at 105 °C to constant mass.

B.9 Determination of the oxidizable constituents

Boil for 3 min, 20,0 ml of the test fluid with 20,0 ml potassium permanganate solution [$c(KMnO_4)$ = 0,002 mol/l] and 1,0 ml sulfuric acid [$c(H_2SO_4)$ = 1 mol/l]. Add 1,0 g of potassium iodide and titrate the solution with sodium thiosulfate solution [$c(Na_2S_2O_3)$ = 0,01 mol/l] until light brown. Then add 5 drops of starch solution and titrate until colourless.

Calculate the consumption of potassium permanganate solution [$c(KMnO_4)$ = 0,01 mol/l] for the test fluid and comparator fluid. The difference between the two values shall not be greater than 1,5 ml.

B.10 Determination of ammonia

Make alkaline 10 ml of the test fluid by the addition of 2 ml of caustic soda [c(NaOH) = 1 mol/l], dilute with distilled water to 15 ml and then add 0,3 ml Nessler's reagent.[2)]

Prepare the comparator solution simultaneously by making alkaline 8 ml of ammonium standard solution [$\rho(NH_4^+)$ = 1 mg/l] by the addition of 2 ml caustic soda [c(NaOH) = 1 mol/l], dilute with distilled water to 15 ml and then add 0,3 ml Nessler's reagent.

After 30 s, examine the solution, which shall not be more strongly yellow-coloured than the comparator solution.

B.11 Determination of metals

The metals Ba, Cd, Cr, Cu, Pb, Sn and Al are determined by atomic absorption spectrometric analysis. The detection limit can be raised by concentrating the test fluid by evaporation in accordance with B.4, in which case 2,5 ml hydrochloric acid solution [ρ(HCl) = 10 g/l] are added to 250 ml test fluid.

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2) See European Pharmacopoeia.

B.12 Testing for heavy metals

Chemical determination of the total of heavy metals can be used instead of the atomic absorption spectrometric determination of metals in the test fluid according to B.4.

Add 1,2 ml thioacetamide reagent to 12 ml of the test fluid and 2 ml ammonium acetate buffer solution (pH = 3,5) and immediately mix.

Prepare the comparator solution produced in the same manner, using 10 ml lead solution [$\rho(Pb^{2+})$ = 2 mg/l] and add 2 ml of the test fluid. After 2 min, examine the solution; it shall not be a deeper shade of brown than the comparator solution.

Annex C
(normative)

Biological tests

C.1 Preparation of the test fluids

C.1.1 General

For biological tests see specific parts of ISO 10993.

C.1.2 Test fluid I (polar extractant)

Fill the empty container twice to nominal capacity with water for injection, shake for approximately 1 min and then empty. After the rinse water has drained off, fill the empty container with enough sterile endotoxin-free sodium chloride solution[3] [ρ(NaCl) = 9 g/l] so that the ratio of the inner surface of the empty container, expressed in square centimetres, to the volume of sodium chloride solution, expressed in ml, is at least 6:1. Then compress the container so that the remaining air escapes from the container, and close it. Extract it for (60 ± 12) min in pressurized, saturated steam at (121 ± 2) °C. Perform the extraction on a sufficient number of containers so that at least approximately 250 ml of extract is available. Mix the extracts from the individual containers after they have cooled. Use 250 ml of the sterile, endotoxin-free isotonic sodium chloride solution used as comparator fluid (blank sample).[4]

If the container is not intended for sterilization at temperatures of at least 121 °C, then the extraction may also be performed at (70 ± 2) °C for a duration of (24 ± 2) h.

C.1.3 Test fluid II (non-polar extractant)

Prepare test fluid II in the same manner as test fluid I according to C.1.2, but:

— dry the empty containers or the plastic pieces after being rinsed with water for injection until moisture can no longer be determined by visual inspection;

— use sesame oil for parenteral use or cottonseed oil as extraction agent;[3]

NOTE If necessary protect the sample from influences of UV light by means of aluminium foil.

— use sesame oil for parenteral use or cottonseed oil as comparator fluid,[4] depending on the extraction agents used;

— if the specific biological test method describes a different test fluid this will supersede the above.

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3) See United States Pharmacopeia (USP).

4) Examples of suitable negative and positive control samples are HD-PE (USP negative bioreaction RS) and PVC with organotin additives (USP positive bioreaction RS), available from US Pharmacopeia, Rockville, MD 20852, USA. This information is given for the convenience of the user of this standard and does not constitute an endorsement by ISO of the product named. Equivalent products may be used if they can be shown to lead to the same results.

C.2 Testing for impermeability to microorganisms

Fill empty containers to their nominal capacity under sterile conditions, with a culture medium, e.g. casein peptone-soybean flour peptone bouillon (CaSo), and seal. Immerse the containers, or the appropriate parts of the containers, in a suspension (~10^6 CFU/ml) of challenge organism (e.g. *Bacillus subtilis*, see national pharmacopoeias) for at least 30 min. Negative controls must not be immersed in the bacterial suspension. Remove the containers from the challenge suspension and rinse with sterile water. Incubate the container for at least 7 d at a temperature appropriate for the challenge organism (e.g. 37 °C for *Bacillus subtilis*). A container that is prepared in the same manner, and the contents of which are inoculated with 1 ml of a culture of challenge organism, serves as the positive control article. Alternatively, prepare the positive control article by compromising a unit filled with culture medium. This may be accomplished by puncturing the particular area of the container being challenged.

Examine the contents for microbial growth. Positive controls shall exhibit turbidity. Test articles shall not be turbid.

C.3 Testing for bacterial endotoxins

Perform tests for bacterial endotoxins according to the relevant pharmacopoeia.

C.4 Testing for cytotoxicity

ISO 10993-5 describes various methods for cytotoxicity testing. The most suitable test should be selected in relation to intended use of the container. Instead of oil test fluid II (see C.1.3) use culture medium with serum or another suitable fluid.

Bibliography

[1] ICH, Harmonized Tripartite Guideline, *Stability Testing of New Drug Substances and Products, Recommended for Adoption on 8 November 2000*, (www.ich.org)

[2] United States Pharmacopeia (USP)

[3] European Pharmacopoeia

[4] Japanese Pharmacopeia

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