INTERNATIONAL STANDARD

ISO 8536-2

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Infusion equipment for medical use —

Part 2:
Closures for infusion bottles

Matériel de perfusion à usage médical —

Partie 2: Bouchons pour flacons de perfusion

Reference number
ISO 8536-2:1992(E)

Contents

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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.

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.

International Standard ISO 8536-2 was prepared by Technical Committee ISO/TC 76, *Transfusion, infusion and injection equipment for medical use*.

ISO 8536 consists of the following parts, under the general title *Infusion equipment for medical use*:

- *Part 1: Infusion glass bottles*
- *Part 2: Closures for infusion bottles*
- *Part 3: Aluminium caps for infusion bottles*
- *Part 4: Infusion sets for single use*
- *Part 5: Burette type infusion sets*
- *Part 6: Freeze drying closures for infusion bottles*
- *Part 7: Caps made of aluminium-plastics combinations for infusion bottles*

Annexes A, B, C and D form an integral part of this part of ISO 8536.

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Infusion equipment for medical use —

Part 2:
Closures for infusion bottles

1 Scope

This part of ISO 8536 specifies the design, dimensions, material, performance requirements and test of closures for infusion bottles as specified in ISO 8536-1.

Closures described herein are intended for single use only.

2 Normative references

The following standards contain provisions which, through reference in this text, constitute provisions of this part of ISO 8536. At the time of publication, the editions indicated were valid. All standards are subject to revision, and parties to agreements based on this part of ISO 8536 are encouraged to investigate the possibility of applying the most recent editions of the standards indicated below. Members of IEC and ISO maintain registers of currently valid International Standards.

ISO 48:1979, *Vulcanized rubbers — Determination of hardness (Hardness between 30 and 85 IRHD).*

ISO 2230:1973, *Vulcanized rubber — Guide to storage.*

ISO 2859-1:1989, *Sampling procedures for inspection by attributes — Part 1: Sampling plans indexed by acceptable quality level (AQL) for lot-by-lot inspection.*

ISO 8536-1:1991, *Infusion equipment for medical use — Part 1: Infusion glass bottles.*

ISO 8536-3:1992, *Infusion equipment for medical use — Part 3: Aluminium caps for infusion bottles.*

ISO 8871:1990, *Elastomeric parts for aqueous parenteral preparations.*

3 Dimensions and designation

3.1 Dimensions

The dimensions of closures shall be as shown in figure 1 and as given in table 1. Figure 1 illustrates two typical designs of closure, types A and B.

Dimensions in millimetres

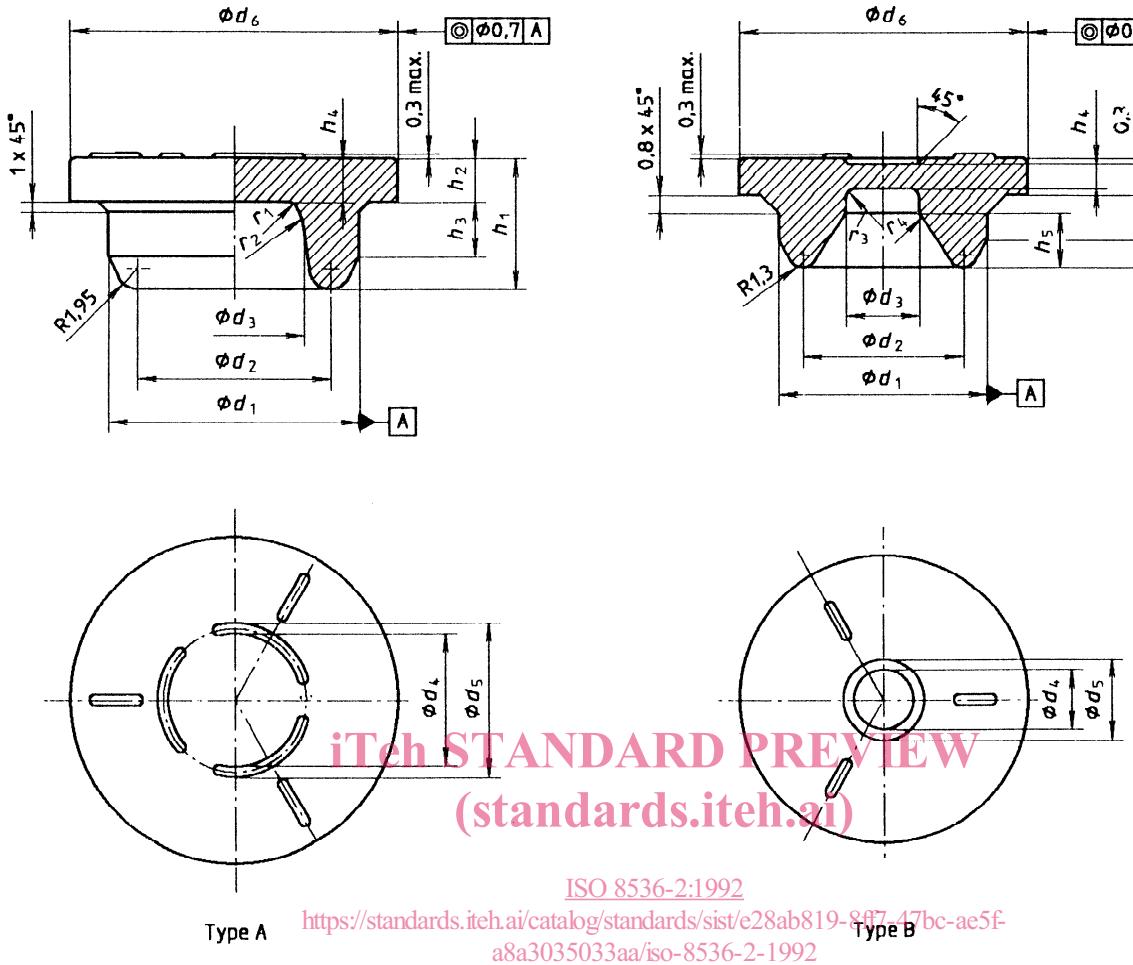

Figure 1 — Dimensions and configuration of types A and B closures

Table 1 — Dimensions of infusion closures

Dimensions in millimetres

Type	Nominal size	d_1 ± 0,1	d_2 max.	d_3 min.	d_4 min.	d_5 max.	d_6 ± 0,3	h_1 ± 0.4	h_2 ± 0,3	h_3	h_4 ± 0,3	h_5	r_1	r_2	r_3	r_4
A	32	23,6	18,2	13	13	14	30,8	12,2	4	5,1	4		1	5	—	—
B	28	19,6	15,5	6,9	6,1	7,1	27,1	10,2	3,4	4,2	2,5	5,1	—	—	1	1

3.2 Designation

Closures are designated according to type: the two types A and B are illustrated in figure 1. The designation is expressed as the number of this part of ISO 8536 followed by the nominal size of the infusion bottle followed by the type letter.

EXAMPLE

A type A closure for infusion bottles of nominal size 32 mm complying with the requirements laid down in this part of ISO 8536 is designated as follows:

Infusion closure ISO 8536-2 - 32 - A

4 Material

The closure shall be made of self-sealing elastomeric material and shall withstand sterilization by autoclaving in saturated steam at (121 ± 2) °C for 1 h without impairment of its function under the conditions of normal use.

5 Physical requirements

5.1 Performance

5.1.1 In order to facilitate the production process, the flange of the closure may have a slightly conical shape (max. 0,8 mm related to the diameter). The trimming edge of the flange shall comply with the acceptable tolerances specified for the diameter of the flange.

5.1.2 All edges of the closure may be rounded.

5.1.3 Sprues, bleeders and injection points shall not be present in the sealing area.

5.1.4 Inside diameter d_3 there may be marks or indentations; outside d_4 there may be spacers, of which the height should not exceed 0,3 mm.

5.1.5 Closures for infusion bottles shall be capable of being hand- or machine-assembled into the opening of the infusion bottles.

5.2 Hardness

The hardness shall be agreed between manufacturer and user. The hardness shall not differ from the nominal value by more than ± 5 IRHD when tested in accordance with ISO 48.

The manufacturer is expected to provide suitable test plates upon request.

5.3 Fragmentation

When tested for fragmentation in accordance with annex A, not more than 20 fragments of diameter equal to or greater than 50 µm per 10 piercings shall be observed.

5.4 Spike penetration force

When tested for penetrability in accordance with annex B, the force needed to penetrate the closure shall not exceed 80 N, and the average value shall be less than 75 N. No closure shall be pushed into the bottle during piercing.

5.5 Sealability and spike retention

When tested in accordance with annex C, complete penetration shall be achieved in all cases and no signs of leakage shall appear between the spike and the closure during 4 h; nor shall the spike be pulled from the closure during this time period.

5.6 Resistance to ageing

The resistance to ageing depends on the actual circumstances of storage and handling. The minimum shelf life of the closure should be agreed upon between closure manufacturer and user.

The useful lifetime of the closure in contact with the pharmaceutical product is part of the compatibility tests to be carried out by the user.

For guidance on storage of vulcanized rubber, see ISO 2230.

6 Chemical requirements

The closure shall be made from the formulation originally tested and approved by the end-user.

The limits specified in table 2 shall be met.

Table 2 — Chemical limits for infusion closures

Test for	Requirement	Test method as described in ISO 8871:1990, annex
Reducing matter (oxidizables)	$\leqslant$ 3,0 ml of $c(KMnO_4) = 2$ mmol/l per 20 ml	C
Heavy metals (calculated as Pb^{2+})	$\leqslant$ 10 µg Pb^{2+}/10 ml	D
Ammonia (calculated as NH_4^+)	$\leqslant$ 20 µg NH_4^+/10 ml	E
Acidity/alkalinity	$\leqslant$ 1,0 ml of c(HCl) or c(NaOH) = 5 mmol/l per 20 ml	G
Residue on evaporation (extracted non-volatile solids)	$\leqslant$ 4 mg/100 ml	H
Volatile sulfides (at pH $\approx$ 2)	coloration of lead acetate paper $\leqslant$ 50 µg Na_2S/20 cm^2 rubber surface	J
Zinc (calculated as Zn^{2+})	Zn^{2+} $\leqslant$ 30 µg/10 ml	K
Conductivity	$\leqslant$ 40 µS/cm	L
Turbidity	not exceeding opalescence suspension number 2	M

7 Biological requirements

The elastomeric closure shall not release any substances which may adversely affect the therapeutic effectiveness of the injectable products, including those substances which may exhibit toxic, pyrogenic or haemolytic reactions.

NOTE 1 Since biological tests are usually requested by most of the national Pharmacopoeias or related regulations of health authorities, they are mandatory for producers and users in countries where they exist.

If this is not the case, a reference needs to be made to biological tests, e.g. as described in the United States Pharmacopoeia, European Pharmacopoeia or other Pharmacopoeias.

8 Sample

Test objects are taken from a suitably collected sample (see ISO 8871:1990, subclause 6.2).

The sample size is deduced from the rules given in ISO 2859-1. However, the minimum sample size, providing a sufficient number of items for all physical and chemical tests, is as follows:

— nominal size 32: 40

— nominal size 28: 50

9 Marking

The packaging closures given shall be marked with the designation given in 3.2.

10 Conformance

The manufacturer of the closure shall certify identity as well as conformance to previously agreed functional parameters or compendium requirements.

Annex A
(normative)

Determination of fragments

A.1 Principle

The purpose of the test is to measure the relative coring tendencies of different ISO rubber closures. The values obtained can be significantly affected by many factors, such as prior processing of the closures, type of crimping device, sealing force, design of the spike, its sharpness, the amount of lubrication of the spike and the keenness of the operator's sight.

It is, therefore, necessary to control these variables in order to obtain comparable results. For this reason, the closures to be tested shall be compared to known samples.

A.2 Apparatus

A.2.1 20 infusion bottles, complying with ISO 8536-1.

A.2.2 Hand-operated capping device and **aluminium caps** with a central hole which fit the infusion bottles to be used in the test.

A.2.3 Membrane filter set.

A.2.4 One test spike, in accordance with annex D.

A.3 Procedure

A.3.1 Degrease the test spike (A.2.4) by means of acetone or methylisobutylketone, and dip it into distilled water. Inspect the spike before use: it shall have its original sharpness and shall not be damaged.

NOTE 2 In case a damaged spike is encountered, use a new spike.

A.3.2 Select 20 infusion bottles (A.2.1) in a size matching the closure to be tested.

Pour n ml of water into each of these bottles, where n is 50 % of the nominal volume of the bottles.

Place a closure of the type to be tested on each of 10 bottles, and a closure with known fragmentation properties on each of the remaining 10 bottles.

Seal all bottles with an aluminium cap (A.2.2) using the hand-operated capping device.

Arrange the bottles in two rows as shown in figure A.1.

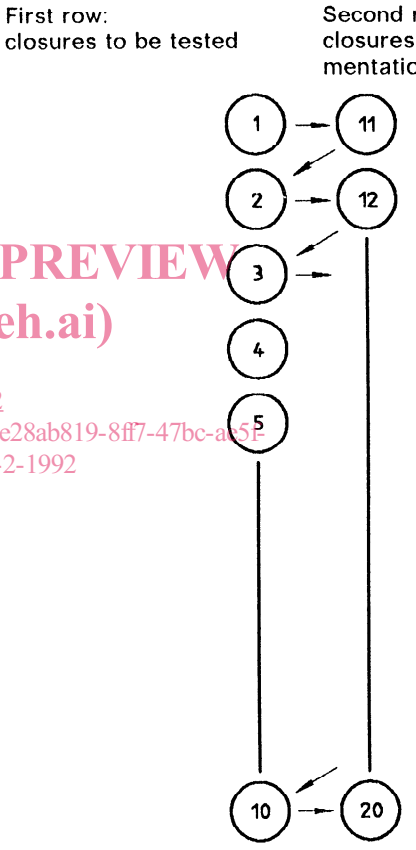

Figure A.1 — Test sequence for fragmentation test

A.3.3 Hold the spike vertically by hand and pierce closure No. 1 within the marked area, holding bottle No. 1 standing firmly in a vertical position. Shake the bottle for a few seconds and withdraw the spike.

After each piercing, repeat the procedure described in A.3.1.