INTERNATIONAL STANDARD

ISO 8536-2

Second edition
2001-06-15

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 8536-2:2001(E)

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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 3.

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 part of ISO 8536 may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

International Standard ISO 8536-2 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 8536-2:1992), which has been technically revised.

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, gravity feed*

— *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 a normative part of this part of ISO 8536.

Introduction

The materials from which injection containers (including elastomeric closures) are made are suitable primary packaging materials for storing injectable products until they are administered.

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 testing 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 normative documents contain provisions which, through reference in this text, constitute provisions of this part of ISO 8536. For dated references, subsequent amendments to, or revisions of, any of these publications do not apply. However, parties to agreements based on this part of ISO 8536 are encouraged to investigate the possibility of applying the most recent editions of the normative documents indicated below. For undated references, the latest edition of the normative document referred to applies. Members of ISO and IEC maintain registers of currently valid International Standards.

ISO 48, *Rubber, vulcanized or thermoplastic — Determination of hardness (hardness between 10 IRHD and 100 IRHD).*

ISO 868, *Plastics and ebonite — Determination of indentation hardness by means of a durometer (Shore hardness).*

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

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

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

ISO 8871-1:—[1)], *Elastomeric parts for parenterals and for devices for pharmaceutical use — Part 1: Extractables in aqueous autoclavates.*

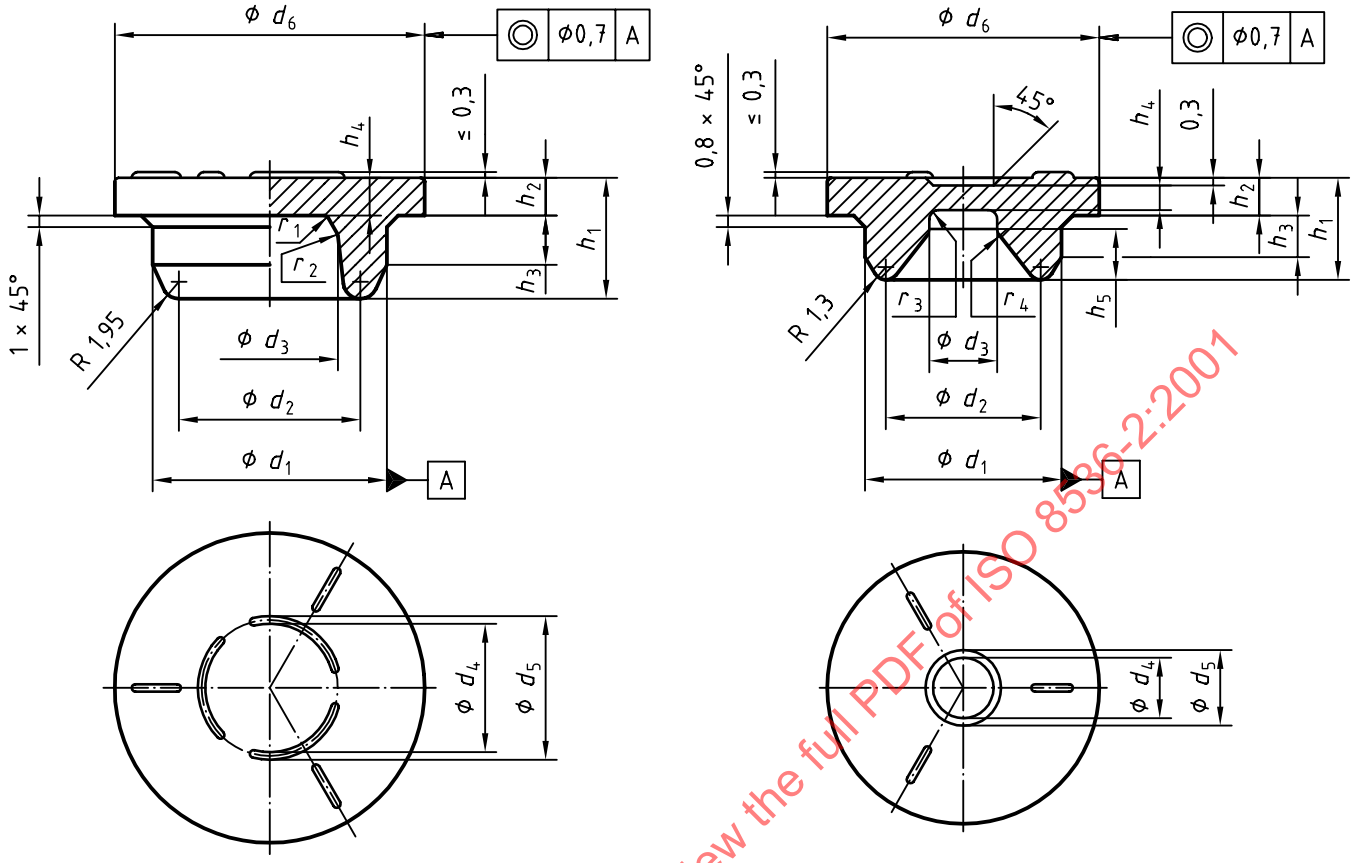
3 Dimensions and designation

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 closures, type A and type B.

1) To be published.

Dimensions in millimetres



Type A Type B

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

Table 1 — Dimensions of infusion closures

Dimensions in millimetres

Type	Nominal size	d_1 ± 0,2	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[a] ± 0,3	h_5
A	32	23,6	18,2	13	13	14	30,8	12,2	4	5,1	4	—
B	28	19,6	15,5	6,9	6,1	7,1	27,1	10,2	3,4	4,2	2,5	5,1

[a] Indentations may reduce the piercing thickness.

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 General

The physical test procedures, described in annexes A, B and C, serve exclusively as comparative type tests of different elastomeric materials and do not enable conclusions to be drawn on the serviceability of closures to be applied. The reason for this is that, in practice, a multitude of different plastic spikes are on the market which do not meet the requirements of the reference steel spike in annex D.

5.2 Performance

5.2.1 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.

5.2.2 All edges of the closure may be rounded.

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

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

5.3 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 or ± 5 Shore A when tested in accordance with ISO 868.

NOTE The manufacturer should provide suitable test plates upon request.

5.4 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 ten piercings shall be observed.

5.5 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.

5.6 Sealability and spike retention

When tested in accordance with annex C, complete penetration shall be achieved (no closure shall be pushed into the bottle) 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.

5.7 Storage

For guidance on storage of vulcanized rubber see ISO 2230.

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

6 Chemical requirements

Chemical requirements are in accordance with ISO 8871-1.

7 Biological requirements

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

8 Sample

A statistically random sample of elastomeric parts to be examined shall be representative for each supply and shall be provided in the original state. The minimum sample size, providing a sufficient number of items for all physical and chemical tests herein, is as follows:

— nominal size 32: 40

— nominal size 28: 40

9 Marking

The packaging of the closures may be marked/labelled 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 this 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. In this context, a subsequent test with closures of known fragmentation properties can be included (reference test), i. e. in a first run the closures of which the fragmentation should be evaluated are tested; immediately afterwards, in a second run, closures with known fragmentation behaviour are tested (reference).

This subsequent testing should be included from time to time to ensure an appropriate handling and test system.

If the fragmentation of the reference samples is found to be in the range of known results, the testing is recognized as valid.

A.2 Apparatus

A.2.1 **Ten infusion bottles,** in accordance with ISO 8536-1. (20 infusion bottles are required should reference testing be included.)

A.2.2 **Capping device** and **aluminium caps** in accordance with ISO 8536-3 and 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.

NOTE The same test spike should be used for all reference and sample testing.

A.3 Procedure

A.3.1 Select ten infusion bottles of a size matching the closures to be tested.

A.3.2 Fill the bottles with a minimum of 50 % of the nominal volume of water.

A.3.3 Place a closure of the type to be tested on each of the ten bottles. Seal all bottles with aluminium caps. Autoclave the bottles in saturated steam for 30 min at (121 ± 2) °C. Remove from autoclave and cool to room temperature.

A.3.4 Degrease the test spike by means of an appropriate organic solvent and dip it into distilled water. Inspect the spike before use; it shall have its original sharpness and shall not be damaged.

A.3.5 Hold the spike vertically by hand and pierce closure No. 1 within the marked area, holding the bottle No. 1 firmly in a vertical position. Shake the bottle for a few seconds and withdraw the spike.

A.3.6 Repeat A.3.4 and A.3.5 until all ten closures are pierced once.

A.3.7 Remove the tested closures from each bottle. Put the content of all the bottles through one membrane filter. Ensure that no fragments remain in the bottles. Count and record the number of fragments in the filter visible with the naked eye under normal conditions, i.e. at a distance between eye and filter of about 25 cm.

NOTE It is assumed that fragments having a diameter larger than 50 µm are visible to the naked eye.

A.3.8 For further identification, the fragments may be examined with a microscope in order to determine size and nature.

A.4 Reference testing

In the case where reference testing is performed, prepare test closures with known fragmentation properties as described in A.3. Use the same test spike.

NOTE Requalification of the system is only valid if, for certain sets of sample testing and reference testing, the same test spike is used.

A.5 Expression of results

Report the recorded number of fragments per ten piercings for the closures to be evaluated.

A.6 Validity

Where reference testing is included, the results obtained on the test closures shall be considered invalid if the results on the known closures lack consistency with previous results, and the reason for such inconsistency shall be investigated.

Annex B
(normative)

Determination of spike penetration force

B.1 Principle

The purpose of this test is to determine the force required to pierce the closure with a spike meeting the requirements of that specified in annex D.

B.2 Apparatus

B.2.1 **Piercing device** which meets the following requirements:

— a spike, clamped in the device, which can be moved perpendicularly at a speed of 200 mm/min. The force exerted backwards on the spike during such movement is indicated or registered in such a way that it can be read with an accuracy of ± 2 N;

— an infusion bottle can be placed in the device in axial alignment, allowing central piercing of the closure on this bottle.

B.2.2 **Two test spikes,** in accordance with annex D.

The spikes are designated as S1 and S2.

B.3 Preparation

B.3.1 Collect a sample of ten closures from the type or lot to be tested.

B.3.2 Prepare ten infusion bottles in accordance with ISO 8536-1, of any size, filled with min. 50 % of the nominal volume of water. Close these ten infusion bottles with closures of the type to be tested.

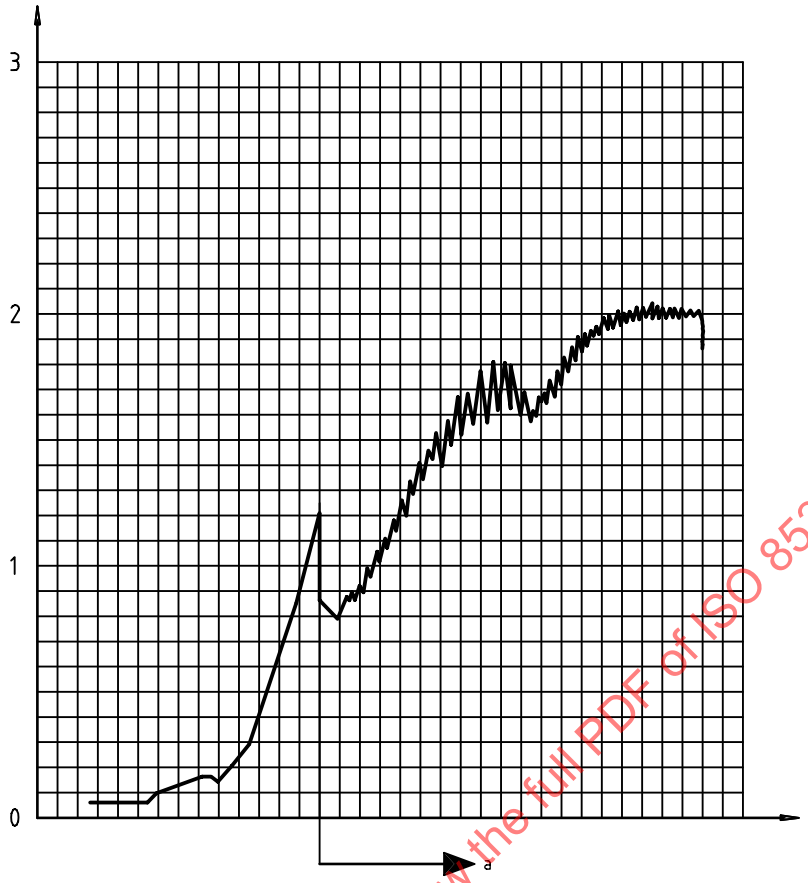
B.3.2 Fix the closures with aluminium caps that meet the requirements of ISO 8536-3. Autoclave the bottles for 30 min at (121 ± 2) °C in saturated steam. Allow them to cool to room temperature.

B.4 Procedure

B.4.1 Degrease spike S1 with an appropriate organic solvent, exerting the utmost care not to blunt it, and clamp spike S1 in the piercing device.

B.4.2 Take the first bottle and remove the tear-off part of the seal so as to have free access to the closure. Place the bottle in the testing device in such a way that the closure will be perforated perpendicularly and centrally.

B.4.3 Operate the device at a speed of 200 mm/min and register the force exerted immediately before penetration takes place (see Figure B.1).



a Required force immediately before piercing

Figure B.1 — Model curve

B.4.4 Restore the clamp to its original position and remove the bottle. Repeat this step with the next four bottles. Degrease the spike before each piercing. Take spike S2 and repeat this step with the remaining five bottles.

B.5 Expression of results

B.5.1 Calculate the average values of penetration force for all ten bottles. Calculate the range of the values of penetration force for all ten bottles.

B.5.2 If the range is larger than 50 N repeat the experiment.

B.5.3 If in the repeated test the range of the results is still above 50 N, repeat the whole experiment using two new spikes.