

# 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)

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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.

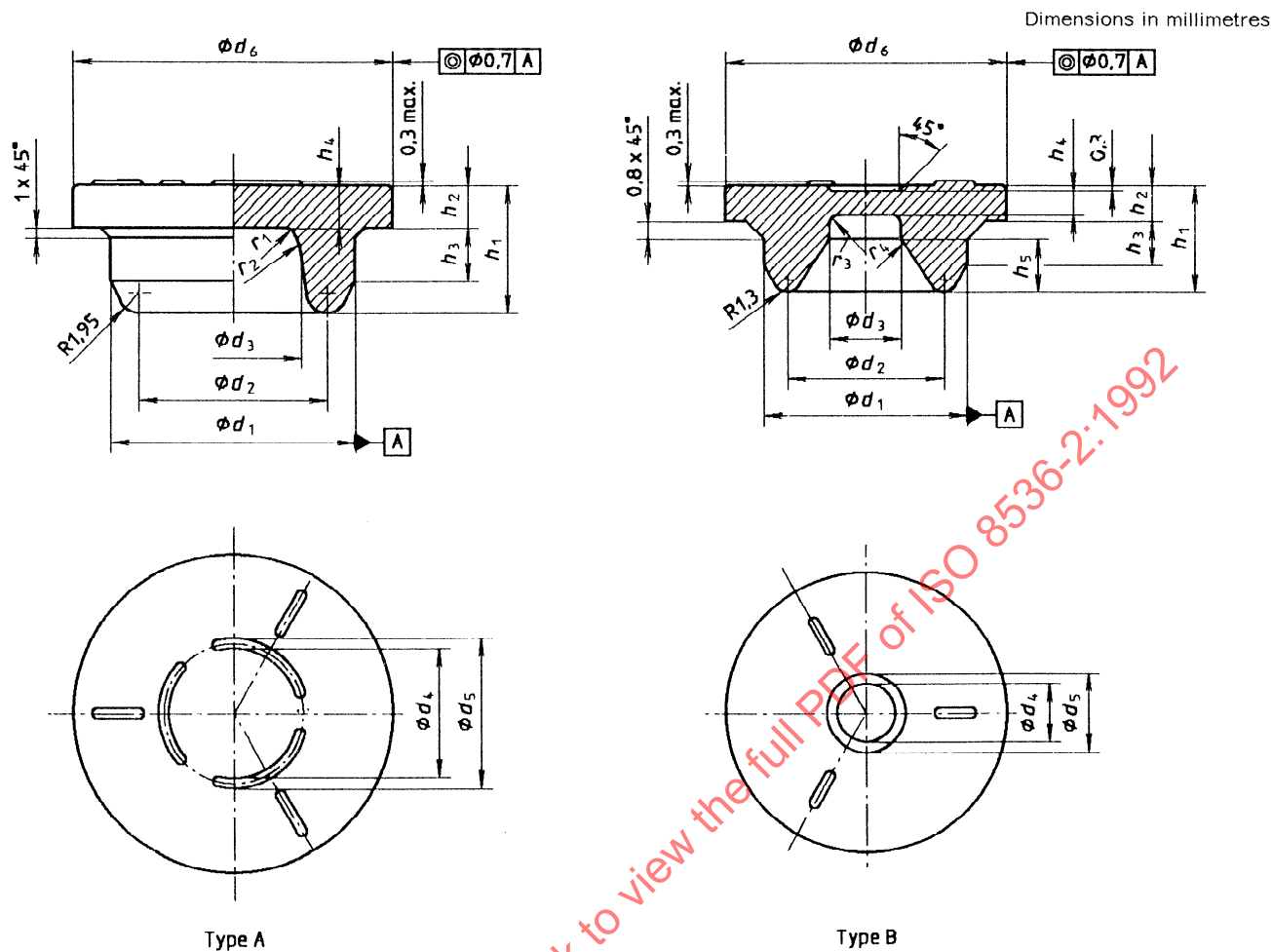


Figure 1 — Dimensions and configuration of types A and B closures

Table 1 — Dimensions of infusion closures

Dimensions in millimetres

| Type | Nominal size | $d_1$<br>$\pm 0,1$ | $d_2$<br>max. | $d_3$<br>min. | $d_4$<br>min. | $d_5$<br>max. | $d_6$<br>$\pm 0,3$ | $h_1$<br>$\pm 0,4$ | $h_2$<br>$\pm 0,3$ | $h_3$ | $h_4$<br>$\pm 0,3$ | $h_5$ | $r_1$ | $r_2$ | $r_3$ | $r_4$ |
|------|--------------|--------------------|---------------|---------------|---------------|---------------|--------------------|--------------------|--------------------|-------|--------------------|-------|-------|-------|-------|-------|
| 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  $(121 \pm 2) ^\circ\text{C}$  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  $d_i$  there may be marks or indentations; outside  $d_o$  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  $\pm 5$  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  $\mu\text{m}$  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)                          | $\leq 3,0$ ml of $c(\text{KMnO}_4) = 2$ mmol/l per 20 ml                                                | C                                                |
| Heavy metals (calculated as $\text{Pb}^{2+}$ )         | $\leq 10$ $\mu\text{g Pb}^{2+}$ /10 ml                                                                  | D                                                |
| Ammonia (calculated as $\text{NH}_4^+$ )               | $\leq 20$ $\mu\text{g NH}_4^+$ /10 ml                                                                   | E                                                |
| Acidity/alkalinity                                     | $\leq 1,0$ ml of $c(\text{HCl})$ or $c(\text{NaOH}) = 5$ mmol/l per 20 ml                               | G                                                |
| Residue on evaporation (extracted non-volatile solids) | $\leq 4$ mg/100 ml                                                                                      | H                                                |
| Volatile sulfides (at pH $\approx 2$ )                 | coloration of lead acetate paper $\leq 50$ $\mu\text{g Na}_2\text{S}/20$ cm <sup>2</sup> rubber surface | J                                                |
| Zinc (calculated as $\text{Zn}^{2+}$ )                 | $\text{Zn}^{2+} \leq 30$ $\mu\text{g}/10$ ml                                                            | K                                                |
| Conductivity                                           | $\leq 40$ $\mu\text{S}/\text{cm}$                                                                       | 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.

First row:  
closures to be tested

Second row:  
closures with known fragmentation properties

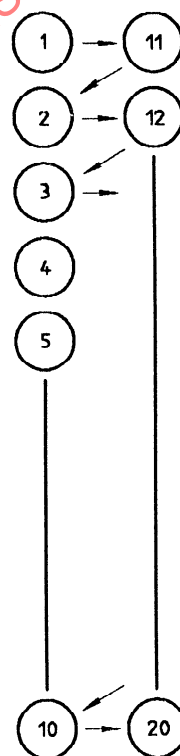


Figure A.1 — Test sequence for fragmentation test

**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.

**A.3.4** Repeat the procedure as described in A.3.3 using closure No. 11 fitted on bottle No. 11 (i.e. the first closure/bottle combination in the second row).

**A.3.5** Repeat all of the procedures described in A.3.3 and A.3.4, using, alternately, bottles from the two rows, until all of the closures have each been pierced once.

**A.3.6** Remove the tested closures from each bottle in the first row. Put the contents of all of the bottles through one membrane filter. Ensure that no fragments remain in the bottles. Count and record the number of rubber fragments on the filter visible with the naked eye under normal conditions, i.e. at a distance between eye and filter of 25 cm.

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

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

**A.3.7** Repeat the procedure described in A.3.6, using, however, the bottles with closures having known fragmentation properties, in the second row.

## **A.4 Expression of results**

Report the recorded numbers of fragments per 10 piercings for the two series.

## **A.5 Validity**

The results obtained on the test closures shall be considered invalid if the results on the known closures lack consistency with previous results; the reason for such inconsistency shall be investigated.

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## Annex B (normative)

### Determination of spike penetration force

#### B.1 Principle

To determine the force required to pierce the closure with a spike that is as specified in annex D.

#### B.2 Apparatus

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

A spike, clamped in the device, can be moved perpendicularly with 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  $\pm 2$  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 10 closures from the type or lot to be tested. Choose these from a lot or type known to yield satisfactory results in practice.

**B.3.2** Prepare 20 infusion bottles in accordance with ISO 8536-1, of any size, half-filled with water. Close 10 infusion bottles with closures of the type to be tested (T) and 10 bottles with the closures of known quality (C).

**B.3.3** Fix the closures with aluminium caps that meet the requirements of ISO 8536-3. Autoclave the bottles for 20 min at  $(121 \pm 1)$  °C in saturated steam. Allow them to cool to room temperature.

#### B.4 Procedure

**B.4.1** Degrease spike S1 with acetone exerting the utmost care not to blunt it and clamp spike S1 in the piercing device.

Take one bottle of type T. Remove the cap 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.

Operate the device at the specified speed and register the force exerted immediately before penetration takes place.

Restore the clamp to its original position and remove the bottle.

**B.4.2** Repeat steps B.4.1, taking a bottle of type C.

**B.4.3** Repeat steps B.4.1 to B.4.2, alternately taking bottles of type T and type C, until five bottles of each type have been tested.

**B.4.4** Repeat steps B.4.1 to B.4.3, using, however, spike S2.

#### B.5 Expression of results

**B.5.1** Calculate average values, AT and AC respectively, for all bottles of type T and for all bottles of type C.

**B.5.2** Calculate the difference between the highest and the lowest value in each of these series (RT and RC respectively).

**B.5.3** If RT and/or RC is larger than 50 N, repeat the whole experiment, using the second set of closure samples.

**B.5.4** If the repetition still fails to result in RT and RC being lower than 50 N, then repeat the whole experiment, using, however, two new spikes.

**B.5.5** If the average value AC is not in accordance with the expectation based on experience, then repeat the whole experiment, using new reference closures as well as new spikes.

## **Annex C**

(normative)

### **Spike retention/sealability**

#### **C.1 Preparation**

**C.1.1** Autoclave 10 closures, not immersed in water, in saturated steam at  $(121 \pm 2) ^\circ\text{C}$  for 20 min.

**C.1.2** Take 10 bottles of 50 ml or 125 ml that meet the requirements of ISO 8536-1. Fill the bottles with the nominal volume of water, close them with the autoclaved closures and secure with aluminium caps according to ISO 8536-3, type A.

#### **C.2 Procedure**

**C.2.1** Place a new spike vertically on the centre of the uncovered part of an unperforated closure, as described in C.1.2.

**C.2.2** Apply a vertical force to the spike. Increase this force until complete penetration has occurred or up to the highest manually achievable value.

**C.2.3** If a complete penetration has been achieved, then fix the bottle vertically with the bottom end up, and attach a total mass of approximately 0,5 kg to the spike. Leave in this situation for 4 h, observe and note any signs of liquid along the spike during this period.

#### **C.3 Expression of results**

**C.3.1** Report the number of cases in which no complete penetration has been achieved, and the number in which leakage along the spike during the observation period has occurred.

**C.3.2** Report the number of cases with complete penetration, and the number in which leakage along the spike during the observation period has occurred.

**C.3.3** Report the number of cases where the spike was not in place after 4 h under stress.