INTERNATIONAL STANDARD

ISO 8536-2

Fourth edition
2023-01

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 8536-2:2023(E)

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Published in Switzerland

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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.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

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. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT), see www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 76, *Transfusion, infusion and injection, and blood processing equipment for medical and pharmaceutical use*, in collaboration with the European Committee for Standardization (CEN) Technical Committee CEN/SS S02, *Transfusion equipment,* in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

This fourth edition cancels and replaces the third edition (ISO 8536-2:2010), which has been technically revised.

The main changes are as follows:

— removal of reference to ISO 7619-1,

— addition of 29 mm size closures to align with ISO 8536-1.

A list of all parts in the ISO 8536 series can be found on the ISO website.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

Primary packaging components made of elastomeric materials are an integral part of medicinal products and thus the principles of current Good Manufacturing Practice (cGMP) apply to the manufacturing of these components.

Principles of cGMP are described in, e.g. ISO 15378 or GMP Guidelines as published by the European Community and the United States of America.

Infusion equipment for medical use —

Part 2:
Closures for infusion bottles

1 Scope

This document specifies the shape, dimensions, material, performance requirements and labelling of closures for infusion bottles as specified in ISO 8536-1.

The dimensional requirements are not applicable to barrier-coated closures.

Closures specified in this document are intended for single use only.

NOTE The potency, purity, stability and safety of a medicinal product during its manufacture and storage can strongly be affected by the nature and performance of the primary packaging.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements 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 48-4, *Rubber, vulcanized or thermoplastic — Determination of hardness — Part 4: Indentation hardness by durometer method (Shore hardness)*

ISO 3302-1, *Rubber — Tolerances for products — Part 1: Dimensional tolerances*

ISO 3302-2, *Rubber — Tolerances for products — Part 2: Geometrical tolerances*

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 8536-7, *Infusion equipment for medical use — Part 7: Caps made of aluminium-plastics combinations for infusion bottles*

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

ISO 8871-4, *Elastomeric parts for parenterals and for devices for pharmaceutical use — Part 4: Biological requirements and test methods*

3 Terms and definitions

No terms and definitions are listed in this document.

ISO and IEC maintain terminology databases for use in standardization at the following addresses:

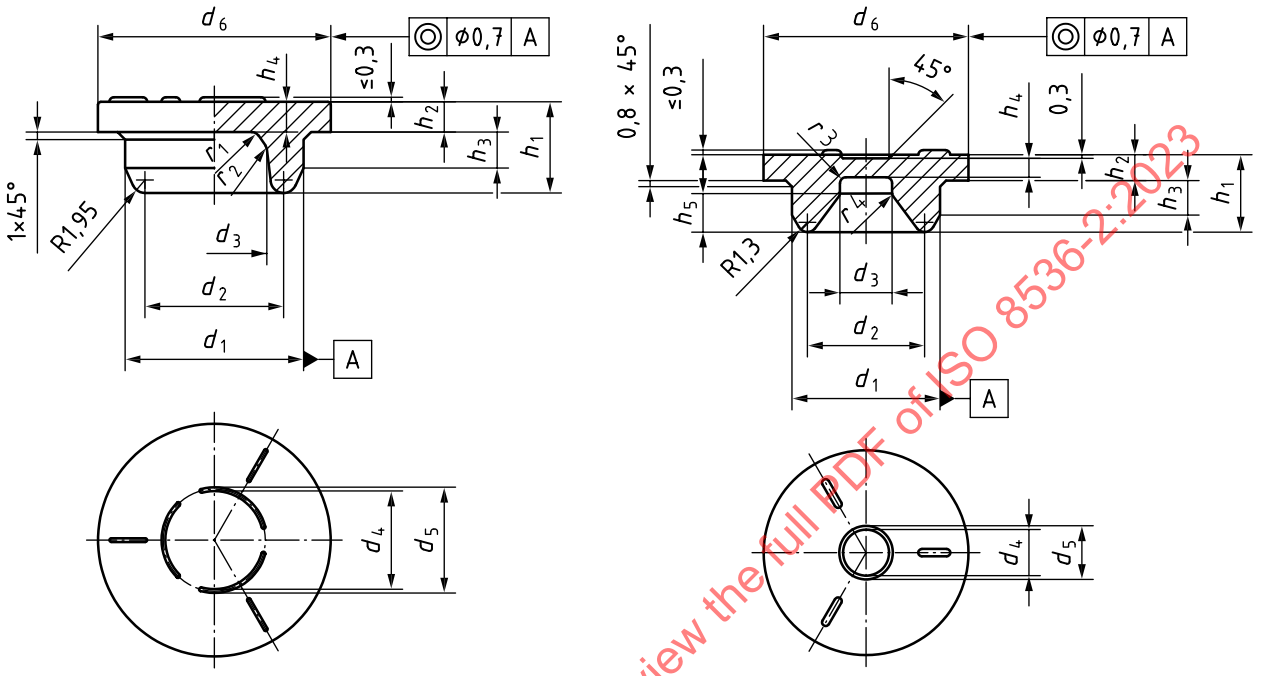
— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at https://www.electropedia.org/

4 Shape and dimensions

4.1 The shape and dimensions of closures shall be in accordance with Figure 1, except for the spacers in Figure 1 for type A and type B closures, and Table 1. Figure 1 illustrates two typical designs of closure, types A and B.

Dimensions in millimetres



a) Type A **b) 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 ±0,25	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	—
	29	17,95	13,38	6,0	5,25	6,8	26,5	11,6 to 12,0	3,8	4,8 to 5,2	2,6 to 3,1	—
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.

4.2 If not otherwise specified, general dimensional tolerances shall be in accordance with ISO 3302-1 and ISO 3302-2.

4.3 In order to facilitate the production process, the flange of the closure may have a slightly conical shape (maximum 0,8 mm related to the diameter).

4.4 The diameter, d_4, which defines the piercing area shall not exceed d_3. Marks and indentations may be placed in the piercing area. The height of the marks shall not exceed 0,3 mm. The spacers in Figure 1 for type A and type B closures are shown for illustrative purposes only and do not form part of the requirements of this document.

4.5 All edges of the closure may be rounded.

5 Designation

Closures can be designated according to their type, see Figure 1. The designation is expressed as the number of this document 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 in accordance with this document is designated as follows:

Infusion closure ISO 8536-2 - 32 - A

6 Material

The elastomeric material used shall meet the requirements in Clause 7.

The elastomeric material shall withstand two sterilization cycles when autoclaving in saturated steam at (121 ± 2) °C for 30 min without exceeding the specified limits and without the impairment of its performance characteristics under the conditions of normal use. In case of other sterilization methods, e.g. irradiation, the suitability of the material shall be evaluated.

For use with infusion solutions, resistance to two steam sterilization cycles may not be needed because only terminal sterilization is applied.

Closures shall be made of elastomeric formulation originally tested and approved by the end-user. The closure manufacturer shall ensure the conformance of each delivery with the type sample and the compliance with previously agreed functional parameters and compendium requirements.

7 Requirements

7.1 General

The requirements specified in 7.2 to 7.4 represent requirements which refer to the condition of the elastomeric closures on receipt by the user.

7.2 Physical requirements

7.2.1 Hardness

The hardness agreed between manufacturer and user shall not differ from the nominal value by more than ±5 International Rubber Hardness Degrees (IRHD, for highly elastic rubbers comparable to Shore A) when tested in accordance with ISO 48-4 on a special test specimen.

7.2.2 Fragmentation

When tested for fragmentation in accordance with Annex A, not more than 20 fragments per ten piercings shall be observed.

7.2.3 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.

7.2.4 Spike retention/sealability

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 over 4 h; nor shall the spike be totally pulled out from the closure during this time period.

7.2.5 Resistance to ageing

The maximum time between the date of manufacture and the pharmaceutical use should be agreed upon between the manufacturer of the closures and the user.

The closures shall maintain their performance characteristics throughout the entire shelf life of the medicinal product that is tested as part of the stability test by the user.

NOTE Ageing depends upon the storage and handling conditions. A guide to storage of vulcanized rubber is given in ISO 2230.

7.3 Chemical requirements

The requirements of ISO 8871-1 shall apply.

7.4 Biological requirements

The requirements of ISO 8871-4 shall apply.

8 Labelling

Packed closures in accordance with this document can be labelled with the manufacturer's name, article description, quantity, date of manufacture, manufacturer's batch number and the designation given in Clause 5. Further labelling should be agreed upon between the manufacturer and the user.

Annex A
(normative)

Determination of fragments

A.1 Principle

The purpose of the test is to measure the 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 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 if reference testing is included).

A.2.2 **Appropriate capping device** and **aluminium or aluminium/plastic caps**, in accordance with ISO 8536-3 or ISO 8536-7, 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.

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

A.2.5 **Steam autoclave**, capable of maintaining (121 ± 2) °C.

A.3 Procedure

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

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

A.3.3 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.

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 of appropriate pore size (e.g. a maximum pore size of 0,8 µm). Ensure that no fragments remain in the bottles. Count and record the number of fragments in the filter visible with naked eye under normal conditions, i.e. at a distance between eye and filter of about 25 cm.

NOTE It is assumed that visibility of particles starts in the size range of 100 µm to 150 µm. The counting of the fragments can be confirmed by measurements made with a microscope having a stage micrometre in order to determine size and nature.

A.4 Reference testing

In case 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 numbers 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 in Annex D.

B.2 Apparatus

B.2.1 **Ten infusion bottles**, in accordance with ISO 8536-1.

B.2.2 **Appropriate capping device** and **aluminium or aluminium/plastic caps**, in accordance with ISO 8536-3 or ISO 8536-7, and which fit the infusion bottles to be used in the test.

B.2.3 **Piercing device**, with the following:

— 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.2.4 **Two test spikes**, in accordance with Annex D.

The spikes are designated as S1 and S2.

B.2.5 **Steam autoclave**, capable of maintaining a temperature of (121 ± 2) °C.

B.3 Procedure

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 a minimum of 50 % of the nominal volume of water. Close these ten infusion bottles with closures of the type to be tested.

B.3.3 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.3.4 Degrease spike S1 with an appropriate organic solvent, exerting the utmost care not to blunt it, and clamp spike S1 in the piercing device.

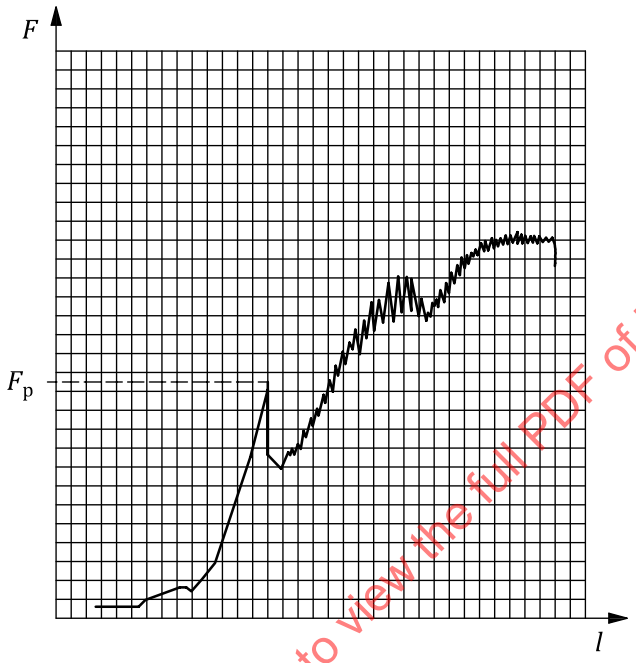
B.3.5 Take the first bottle and remove the tear-off part of the seal to have free access to the closure. Place the bottle in the testing device in such a way that the closure will be perforated perpendicularly and centrally.

B.3.6 Operate the device at a speed of 200 mm/min and register the force exerted immediately before penetration takes place (see Figure B.1).

B.3.7 Restore the clamp to its original position and remove the bottle.

B.3.8 Repeat B.3.1 to B.3.4 with the next four bottles.

B.3.9 Take spike S2 and repeat B.3.1 to B.3.4 with the remaining five bottles.



Key

F force exerted on the spike, in newtons

F_p force exerted at the moment when the spike pierces the closure

l movement of the spike, in millimetres

Figure B.1 — Model curve

B.4 Expression of results

B.4.1 Calculate the average values of penetration force (F_p) for all ten bottles. Calculate the range of the values of penetration force (F_p) for all ten bottles.

B.4.2 If the range is larger than 50 N, repeat the experiment.

B.4.3 If, in the repeated test, the range of the results is still above 50 N, repeat the whole experiment using two new spikes.

Annex C
(normative)

Spike retention/sealability

C.1 Principle

The purpose of this test is to determine the capability of the stopper to retain a spike and to seal properly around it.

C.2 Apparatus

C.2.1 **Ten infusion bottles**, in accordance with ISO 8536-1.

C.2.2 **Appropriate capping device** and **aluminium or aluminium/plastic caps**, in accordance with ISO 8536-3 or ISO 8536-7, and which fit the infusion bottles to be used in the test.

C.2.3 **Test spikes**, in accordance with Annex D.

C.2.4 **Steam autoclave**, capable of maintaining (121 ± 2) °C.

C.3 Procedure

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

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

C.3.3 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.

C.3.4 Place the spike, vertically on the centre of the uncovered part of an unperforated closure as prepared in C.3.2 and C.3.3.

C.3.5 Apply a vertical force to the spike. Increase this force until complete penetration has occurred or up to the highest manually achievable value.

C.3.6 If complete penetration has been achieved, fix the bottle vertically with the bottom end up, and attach a total mass of (0,5 ± 0,025) 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.4 Expression of results

C.4.1 Report the number of cases where the spike is still inserted in the rubber stopper, but has moved from its original position, and the number where leakage along the spike during the observation period has occurred, after 4 h under stress.

C.4.2 Report the number of cases where the spike has not moved from its original position in the rubber stopper and the number where leakage along the spike during the observation period has occurred, after 4 h under stress.

C.4.3 Report the number of cases where the spike was totally pulled out from the rubber stopper after 4 h under stress.