
**Infusion equipment for medical use —
Part 6:
Freeze drying closures for infusion
bottles**

Matériel de perfusion à usage médical —

Partie 6: Bouchons à lyophilisation pour flacons de perfusion

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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 8536-6 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 8536-6:1995), which has been technically revised in order to align this part of ISO 8536 with ISO 8871-1, ISO 8871-4 and ISO 8871-5.

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 infusion sets for single use, gravity feed*
- *Part 6: Freeze drying closures for infusion bottles*
- *Part 7: Caps made of aluminium-plastics combinations for infusion bottles*
- *Part 8: Infusion equipment for use with pressure infusion apparatus*
- *Part 9: Fluid lines for use with pressure infusion equipment*
- *Part 10: Accessories for fluid lines for use with pressure infusion equipment*
- *Part 11: Infusion filters for use with pressure infusion equipment*
- *Part 12: Check valves*

Introduction

Freeze drying closures are put on the top of infusion bottles after filling, leaving sufficient openings for the sublimation process and vacuum. At the end of the drying process they can be fully inserted into the glass container by hydraulic or mechanical means in the vacuum chamber.

Freeze drying closures can pick up water during shipping, storage, washing and steam sterilization cycles, which is difficult to remove in a subsequent drying cycle. As a consequence, the freeze drying closures are usually loaded with residual moisture. Depending upon the mass of the freeze dried product and the degree of its sensitivity to water, the residual moisture in the rubber material can spoil the freeze dried preparation during storage.

These specific process requirements have been addressed in this part of ISO 8536 by specifying relevant requirements for freeze drying closures including a test method on determination of residual moisture.

Primary packaging components made of elastomeric materials are an integral part of medicinal products and thus the principles of current Good Manufacturing Practices (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.

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Infusion equipment for medical use —

Part 6: Freeze drying closures for infusion bottles

1 Scope

This part of ISO 8536 specifies the shape, dimensions, material, performance requirements and labelling for the type of closure for infusion bottles, as described in ISO 8536-1, which are used in connection with the freeze drying (or lyophilization) of drugs and biological materials.

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

Closures specified in this part of ISO 8536 are intended for single use only.

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

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

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

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

ISO 7619-1, *Rubber, vulcanized or thermoplastic — Determination of indentation hardness — Part 1: Durometer method (Shore hardness)*

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, *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*

ISO 8871-5:2005, *Elastomeric parts for parenterals and for devices for pharmaceutical use — Part 5: Functional requirements and testing*

3 Terms and definitions

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

3.1 freeze drying lyophilization

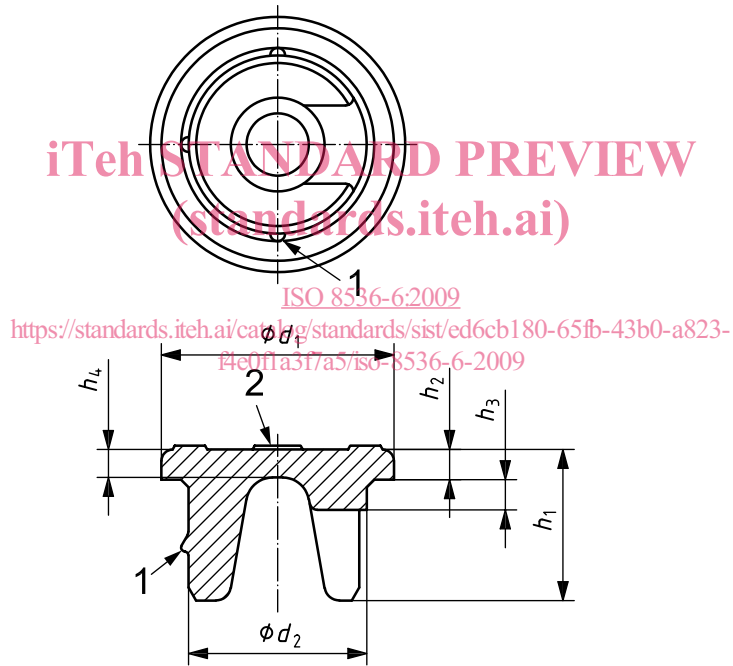
drying process designed to remove solvents from both aqueous and non-aqueous systems by sublimation and desorption

3.2 freeze drying closure

closure that enables the drying of a frozen pharmaceutical preparation in a vacuum chamber

4 Shape and dimensions

4.1 The dimensions of freeze drying closures shall be as given in Table 1. Figure 1 illustrates the general design of a freeze drying closure.



Key

- 1 positioning element
- 2 spacers

NOTE The total height of the freeze drying closure, h_1 , can vary and is subject to mutual agreement between manufacturer and user.

Figure 1 — Example to illustrate a freeze drying closure design

Table 1 — Dimensions of freeze drying closures

Dimensions in millimetres

Nominal size	d_1	d_2^a	h_2	h_3	h_4
	$\pm 0,2$	$\pm 0,1$	$\pm 0,3$	min.	min.
32	30,8	23,6	4,0	4	3,7
28	27,1	19,6	3,4	4	2,2

^a The value of d_2 is applied in that area which is defined by h_3 .

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

4.3 If spacers are located on the top of the flange, they shall not interfere with the marks for the injection site. The height of the spacers shall not exceed 0,3 mm.

On the top surface there may be marks or indentations.

4.4 If the flange of the closure has a slightly conical shape, it shall be 0,8 mm maximum in relation to the diameter in order to facilitate production. The tolerances of the trimming edge of the flange shall comply with the tolerances specified in Table 1 for the diameter d_1 .

4.5 The plug part shall provide slits, channels or other appropriate means in conjunction with protruding or positioning elements at the outer diameter, which enable insertion in a drying (halfway) position during the sublimation process.

4.6 The design of the positioning elements to hold the freeze drying closure firmly in the sublimation position should not compromise the full insertion of the closure.

4.7 The design of the flange part in conjunction with the plug design shall permit both the reconstitution of the freeze dried product with the appropriate solvent and the removal of the dissolved product by means of a piercing device.

4.8 The freeze drying closure shall be designed and manufactured in such a way that the removal of the reconstituted product with a hypodermic needle can be visually controlled in order to minimize the amount of residual product.

4.9 When freeze drying closures are put in place for the lyophilization process and the container is exposed to transport processes, they should exhibit sufficient shock and vibration resistance so that under regular processing conditions they do not fall off or become distorted.

4.10 All edges of the closure may be rounded.

5 Designation

A freeze drying closure for infusion bottles can be designated by the words “freeze drying closure” followed by the number of this part of ISO 8536 followed by the nominal size.

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

Freeze drying closure ISO 8536-6 - 32

6 Material

The elastomeric material used shall meet the requirements specified 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 has to be evaluated.

With regard to the special requirement for low residual moisture, the drying process shall be included in the evaluation of the material's performance characteristics (see also 7.2.7).

Closures shall be made from the 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 and compendium requirements.

NOTE It is current practice to prefer elastomeric materials that use straight or halogenated butyl rubbers as a base polymer, since this class of materials exhibits an excellent barrier function against water vapour and gas permeation.

7 Requirements

7.1 General

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

7.2 Physical requirements

7.2.1 Hardness

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The hardness agreed upon between manufacturer and user shall not differ from the nominal value by more than ± 5 Shore A when tested in accordance with ISO 7619-1 on a special test specimen. Alternatively, the hardness can be tested on the closures in accordance with ISO 48. If tested in accordance with ISO 48, the microhardness shall not differ by more than ± 5 IRHD from the type sample.

7.2.2 Fragmentation (coring)

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.

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 penetration/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 pulled from the closure during this time period.

7.2.5 Self-sealing and container closure seal integrity

The requirements of ISO 8871-5:2005, 4.3 shall apply using vials in accordance with ISO 8536-1 for the test.

7.2.6 Container closure seal integrity

The requirements of ISO 8871-5:2005, 4.4 shall apply using vials in accordance with ISO 8536-1 for the test. If the test specimen complies with 7.2.5, these requirements have also been met and a separate testing according to this subclause is not needed.

7.2.7 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.

7.2.8 Residual moisture

Upon request, the rubber manufacturer shall give a recommendation at what time and temperature (time/temperature profile) the user can reduce residual moisture from freeze drying closures to end up with a pre-defined moisture level, as exposure to dry heat may damage the elastomeric material.

Residual moisture can be determined in accordance with Annex E.

7.3 Chemical requirements

The requirements given in ISO 8871-1 shall apply.

7.4 Biological requirements

The requirements given in ISO 8871-4 shall apply.

8 Labelling

Packed closures which meet the requirements of this part of ISO 8536 can be labelled with the designation given in Clause 5.