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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.

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 on 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 the following URL: www.iso.org/iso/foreword.html.

The committee responsible for this document is ISO/TC 76, *Transfusion, infusion and injection, and blood processing equipment for medical and pharmaceutical use*.

This third edition cancels and replaces the second edition (ISO 8536-6:2009), which has been technically revised.

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

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 document 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, for example, ISO 15378 or GMP Guidelines as published by the European Community and the United States of America.

Infusion equipment for medical use —

Part 6:
Freeze drying closures for infusion bottles

1 Scope

This document specifies the shape, dimensions, material, performance requirements and labelling for the type of closure for infusion bottles, as described in ISO 8536-1, that is 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 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 3302 (all parts), *Rubber — Tolerances for products*

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*

3 Terms and definitions

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

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

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

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

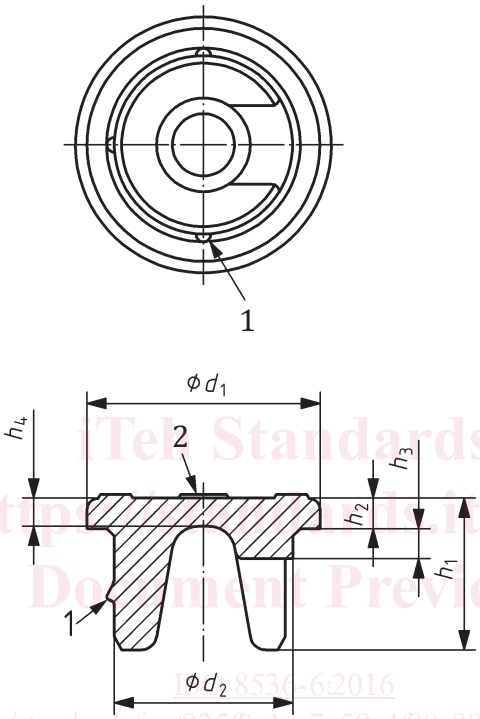
3.1
freeze-drying
lyophilization
drying process designed to remove solvents from both aqueous and non-aqueous systems by sublimation and desorption

3.2
freeze drying closure
closure which 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.

Dimensions in millimetres



Key

1 positioning element

2 spacers

NOTE The total height of the freeze drying closure, h_1, may 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 ±0,3	d_2[a] ±0,2	h_2 ±0,3	h_3 min.	h_4 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 (all parts).

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 slight conical shape, the conicity shall be 0,8 mm max. 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 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 that under regular processing conditions they do not fall off nor become distorted.

4.9 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 document 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 document 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 shall 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 7.2.5).

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 which 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

The hardness agreed 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 special test specimen. Alternatively, the hardness can be tested on the closures according to ISO 48. If tested according to 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 10 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 for a period 4 h; nor shall the spike be pulled 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 which 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.

7.2.6 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 in ISO 8871-1 shall apply.