INTERNATIONAL STANDARD

ISO 8362-5

Third edition
2016-02-15

Injection containers and accessories —

Part 5: Freeze drying closures for injection vials

Récipients et accessoires pour produits injectables —

Partie 5: Bouchons à lyophilisation pour flacons d'injection

Reference number
ISO 8362-5:2016(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.

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).

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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 WTO principles in the Technical Barriers to Trade (TBT) see the following URL: Foreword - Supplementary information.

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 8362-5:2008), which has been technically revised to include a new 7.5.

ISO 8362 consists of the following parts, under the general title *Injection containers and accessories*:

— *Part 1: Injection vials made of glass tubing*

— *Part 2: Closures for injection vials*

— *Part 3: Aluminium caps for injection vials*

— *Part 4: Injection vials made of moulded glass*

— *Part 5: Freeze drying closures for injection vials*

— *Part 6: Caps made of aluminium-plastics combinations for injection vials*

— *Part 7: Injection caps made of aluminium-plastics combinations without overlapping plastics part*

Introduction

Freeze drying closures are put on the top of a glass container after filling, leaving sufficient openings for the sublimation process and vacuum. At the end of the drying process, they are 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 8362 by specifying relevant requirements for freeze drying closures, including a test method for determining 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, for instance, in ISO 15378 or in the GMP Guidelines as published by the European Community and the United States of America.

Injection containers and accessories —

Part 5:
Freeze drying closures for injection vials

1 Scope

This part of ISO 8362 specifies the shape, dimensions, material, performance requirements and labelling for the type of closure for injection vials, as described in ISO 8362-1 and ISO 8362-4, which 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 part of ISO 8362 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 documents, in whole or in part, are normatively referenced in this document and are indispensable for its application. 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 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 given in Table 1 while Figure 1 illustrates the general design of a freeze drying closure.

Table 1 — Dimensions of freeze drying closures

Dimensions in millimetres

Nominal size	d_1 ±0,2	d_2[a] min.	h_2 ±0,25	h_3 min.	h_4 min.
13	12,5	7,5	2,0	2,0	1,8
20	18,8	13,0	3,3	2,0	2,0

[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 piercing area (see Figure 1). The height of the spacers shall not exceed 0,3 mm.

NOTE The spacers in Figure 1 are shown for illustrative purposes only and do not form part of the requirements of this part of ISO 8362.

There may be marks or indentations on the top surface.

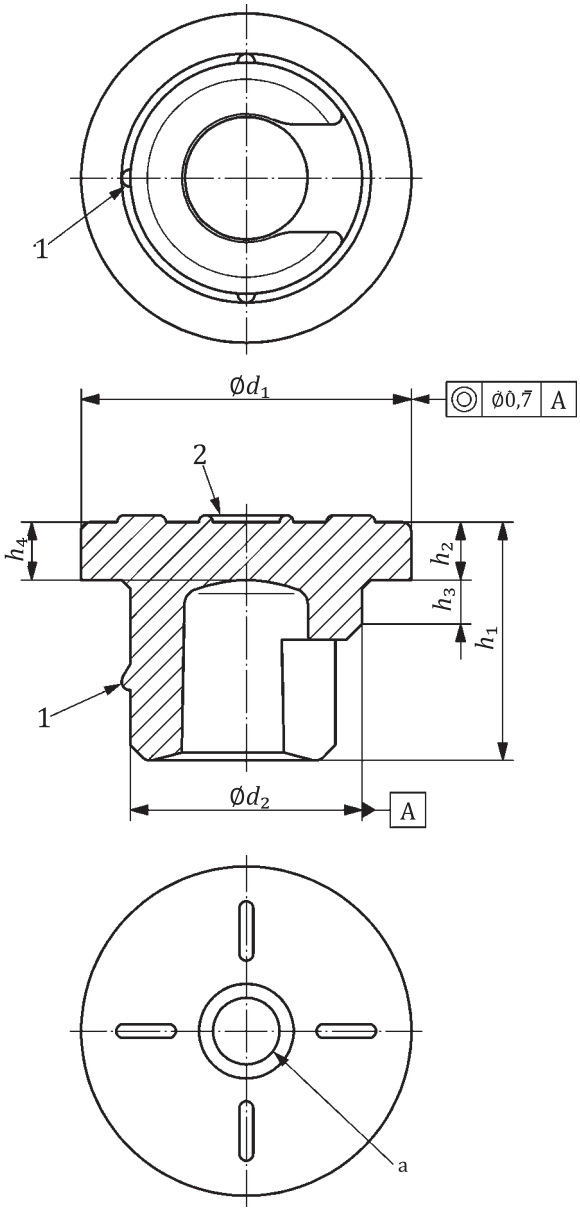
4.4 If the flange of the closure has a slightly conical shape, it shall be 0,3 mm maximum in relation to the diameter in order to facilitate production. The tolerances of the trimming edge of the flange shall comply with the tolerances specified in Table 1 for diameter d_1.

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 on a drying (halfway) position during the sublimation process.

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

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.

Dimensions in millimetres



Key

1 positioning element

2 spacer

a The inner diameter shall not be wider than the inner lumen.

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 of a freeze drying closure design

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 transportation processes, they should exhibit sufficient shock and vibration resistance that, under regular processing conditions, they do not fall off or become distorted.

5 Designation

A freeze drying closure for injection vials can be designated by the words “freeze drying closure” followed by the number of this part of ISO 8362 followed by the nominal size.

EXAMPLE A freeze drying closure of nominal size 13 complying with the requirements laid down in this part of ISO 8362 is designated as follows:

Freeze drying closure ISO 8362–5 — 13

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 impairment of its performance characteristics under conditions of normal use. In case other sterilization methods are used, 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 7.2.7).

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 compendial 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 Performance 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 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 Penetrability

The requirements of ISO 8871-5:2005, 4.1 shall apply.

7.2.3 Fragmentation

The requirements of ISO 8871-5:2005, 4.2 shall apply.

7.2.4 Self-sealing and aqueous solution tightness

The requirements of ISO 8871-5:2005, 4.3 shall apply.

7.2.5 Aqueous solution tightness

The requirements of ISO 8871-5:2005, 4.4 shall apply. If the test specimen complies with 7.2.4, the requirements of this subclause have also been met and separate testing according to this subclause is not needed.

7.2.6 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. Guidelines for storage of vulcanized rubber are given in ISO 2230.

7.2.7 Residual moisture

Upon request, the rubber manufacturer shall give a recommendation as to the time and temperature (time/temperature profile) at which 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 A.

7.3 Chemical requirements

The requirements in ISO 8871-1 shall apply.

7.4 Biological requirements

The requirements in ISO 8871-4 shall apply.

7.5 Particulate contamination requirements

Closures should be manufactured such that particulate contamination is minimized. The specification and method should be agreed upon by the manufacturer of the closure and the user. It is recommended that closures be tested in accordance with ISO 8871-3.

8 Labelling

Packed closures that meet the requirements of this part of ISO 8362 can be labelled with the designation given in Clause 5.

Annex A
(informative)

Determination of moisture

A.1 Principle

The elastomeric material to be tested is heated in a nitrogen stream in a drying pistol. The evaporated water is passed into a titration cell where the amount of water is determined coulometrically.

A.2 Apparatus

A.2.1 Karl-Fischer coulometric device.

A.2.2 Drying pistol, with a heating system to adjust temperatures between 110 °C and 150 °C.

A.2.3 Nitrogen supply, with a molecular sieve cartridge.

A.2.4 Stainless steel weighing boat.

A.2.5 Analytical balance, accurate to 0,1 mg.

A.3 Reagents

The reagents are as specified in the measurement system manual.

A.3.1 Sodium tartrate, or equivalent, with known water content (standard).

A.3.2 Control solution, 1 % (by mass) water in organic solvent.

A.4 Procedure

A.4.1 Apparatus preparation

Set up the apparatus as indicated in the instruction manual. Adjust the drying pistol to (140 ± 2) °C and flush it with nitrogen at a suitable rate.

Check the apparatus in particular for the following:

— low blank drift;

— correct determination of water content of control solution;

— constant slope of cumulative graph water/time when running a blank;

— correct determination of water in sodium tartrate.

Daily checking is recommended.

A.4.2 Sample preparation

A.4.2.1 General

Use pincers or wear disposable gloves when handling the closures.

Maintain the untreated closures in their original packing and keep treated closures in airtight vessels with a headspace as small as possible.

Handle closures at (23 ± 2) °C and (50 ± 5) % relative humidity (see ISO 554).

A.4.2.2 Preparing elastomeric material for determination

Collect at least 10 closures and cut from each closure at least one segment from the top flange along a perpendicular plane such that the segment length is approximately 4 mm to 7 mm (see Figure A.1).

Put all these segments in the weighing boat, taking segments from all closures. Weigh to an accuracy of 0,1 mg. The suitable amount of elastomeric material depends on water content and the determination unit which is used (see A.6).

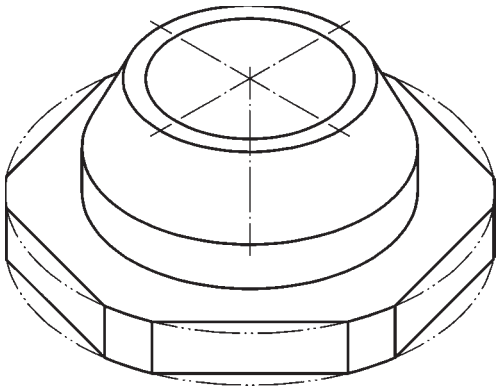


Figure A.1 — Cutting segments from closures

A.4.3 Determination

Put the segments into the drying pistol immediately after weighing and start the determination.

Record the values obtained as a cumulative curve of water content versus time until a constant slope of the curve is reached. Double determination is recommended.

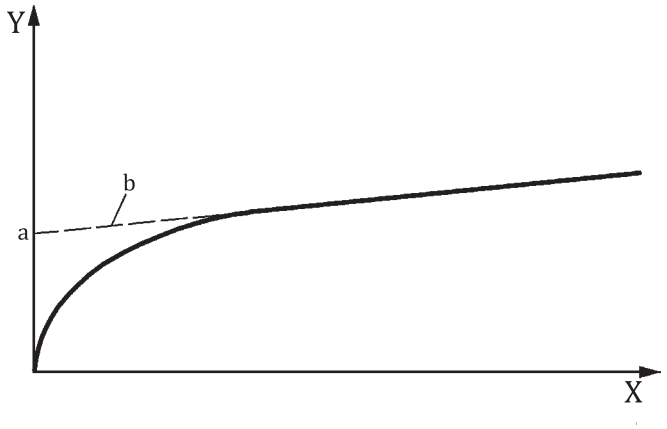
A.5 Calculation and expression of results

A.5.1 Extrapolation

Figure A.2 shows schematically the cumulative curve as recorded during determination.

For extrapolation, use the line drawn through the values at for example 90 min, 85 min, 80 min, 75 min and 70 min.

Read the results as micrograms of water from the graph by extrapolation of the curve, as shown in Figure A.2.



Key

X time, in minutes

Y amount of water, in micrograms

a Amount of water of the specimen, in micrograms, obtained by extrapolation of the curve.

b Line received by extrapolation.

Figure A.2 — Cumulative curve water/time

A.5.2 Expression of results

The amount of water, *W*, shall be indicated as a percentage by mass of moisture of the rubber segments in the drying pistol, as given in Formula (A.1):

$$W = \frac{m_1}{m_2 \times 10} \tag{A.1}$$

where

m_1 is the mass of water, in micrograms, determined by extrapolation of the curve;

m_2 is the mass of rubber segments in the drying pistol, in milligrams.

A.6 Comments and limitations

A.6.1 A persistent decrease in slope at the end part of the curve may be the result of the following factors:

— apparatus drift, including residual moisture in the carrier gas;

— side reactions with volatile ingredients or decomposition products from the material tested;

— slow diffusion from the inner area of the rubber parts tested.

Back-extrapolation will compensate for the effects of drift and other influences.

Slow diffusion is countered by minimizing the thickness of the material tested.

A.6.2 For expected moisture contents between 0,1 % and 1,5 %, a suitable sample weight is 200 mg to 400 mg, corresponding to 500 µg and 3 000 µg of water

Bibliography

[1] ISO 554, *Standard atmospheres for conditioning and/or testing — Specifications*[1)]

[2] ISO 2230, *Rubber products — Guidelines for storage*

[3] ISO 15378, *Primary packaging materials for medicinal products — Particular requirements for the application of ISO 9001:2000, with reference to Good Manufacturing Practice (GMP)*

1) This is a withdrawn standard.

ICS 11.040.20

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