
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.

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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

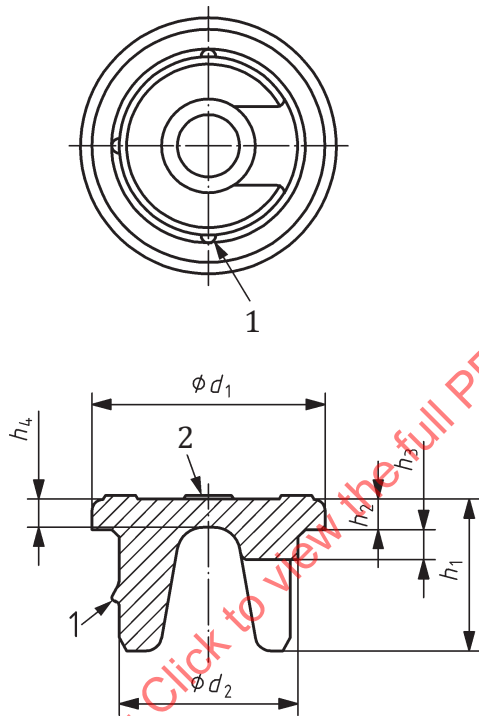
3.2
freeze drying closure

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 $\pm 0,3$	d_2^a $\pm 0,2$	h_2 $\pm 0,3$	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 $(121 \pm 2)^\circ\text{C}$ 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.

7.4 Biological requirements

The requirements in ISO 8871-4 shall apply.

8 Labelling

Packed closures which meet the requirements of this document can be labelled with the designation given in [Clause 5](#).

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Annex A (normative)

Determination of fragments

A.1 Principle

The purpose of the test is to measure the relative coring tendencies of different 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 functioning of the 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 are required, should reference testing be included).

A.2.2 Capping device and aluminium caps in accordance with ISO 8536-3, 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 to maintain $(121 \pm 2) ^\circ\text{C}$.

A.3 Procedure

A.3.1 Collect a sample of 10 closures from the type or lot to be tested. Subject the closure to steam sterilization for 30 min at $(121 \pm 2) ^\circ\text{C}$, followed by drying for 16 h at $70 ^\circ\text{C}$.

NOTE If the closures in practice are subjected to a sterilization process other than steam sterilization, use that sterilization process to sterilize the closures and disregard [B.3.1](#).

A.3.2 Prepare 10 infusion bottles in accordance with ISO 8536-1, of any size, filled with min. 50 % of the nominal volume of water. Close these 10 infusion bottles with sterilized closures of the type to be tested.

A.3.3 Fix the closures with aluminium caps that meet the requirements of ISO 8536-3.

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 10 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. Ensure that no fragments remain in the bottles. Count and record the number of fragments in the filter visible with the naked eye under normal conditions, i.e. at a distance between eye and filter of about 25 cm.

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

A.3.8 For further identification, the fragments may be examined with a microscope in order to determine size and nature.

A.4 Reference testing

If 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 one set of sample testing and reference testing, the same test spike is used.

A.5 Expression of results

Report the recorded numbers of fragments per 10 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. 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 of that specified in [Annex D](#).

B.2 Apparatus

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

B.2.2 Capping device and aluminium caps in accordance with ISO 8536-3, and which fit the infusion bottles to be used in the test.

B.2.3 Piercing device which meets the following criteria.

- 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 to maintain $(121 \pm 2) ^\circ\text{C}$.

B.3 Procedure

B.3.1 Collect a sample of 10 closures from the type or lot to be tested. Subject the closure to steam sterilization for 30 min at $(121 \pm 2) ^\circ\text{C}$, followed by drying for 16 h at $70 ^\circ\text{C}$.

NOTE If the closures in practice are subjected to a sterilization process other than steam sterilization, use that sterilization process to sterilize the closures and disregard [B.3.1](#).

B.3.2 Prepare 10 infusion bottles in accordance with ISO 8536-1, of any size, filled with min. 50 % of the nominal volume of water. Close these 10 infusion bottles with sterilized closures of the type to be tested.

B.3.3 Fix the closures with aluminium caps that meet the requirements of ISO 8536-3.

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

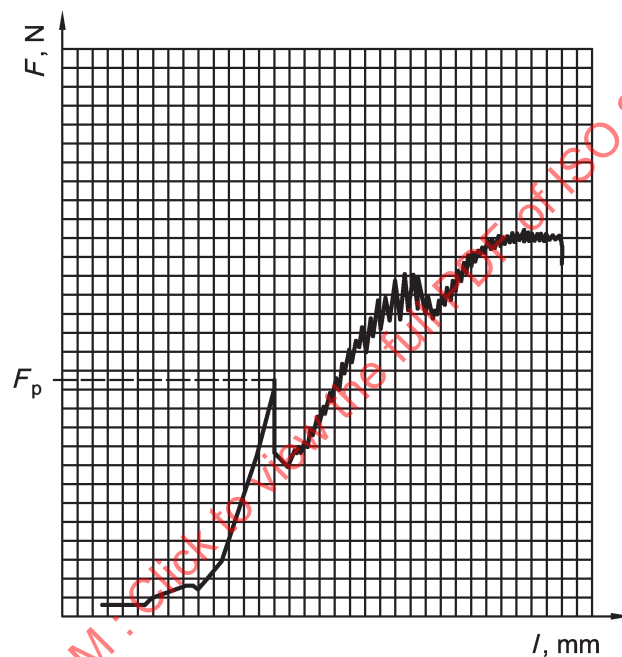
B.3.5 Take the first bottle and remove the tear-off part of the seal so as to have free access to the closure. Place the bottle in the testing device in such a way that the closure will be perforated perpendicularly and centrally.

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

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

l movement of the spike

Figure B.1 — Model curve

B.4 Expression of results

B.4.1 Calculate the average values of penetration force for all 10 bottles. Calculate the range of the values of penetration force for all 10 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 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 Capping device and aluminium caps in accordance with ISO 8536-3, 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 to maintain $(121 \pm 2) ^\circ\text{C}$.

C.3 Procedure

C.3.1 Collect a sample of 10 closures from the type or lot to be tested. Subject the closures to steam sterilization for 30 min at $(121 \pm 2) ^\circ\text{C}$, followed by drying for 16 h at $70 ^\circ\text{C}$.

NOTE If the closures in practice are subjected to a sterilization process other than steam sterilization, use that sterilization process to sterilize the closures and disregard [B.3.1](#).

C.3.2 Prepare 10 infusion bottles in accordance with ISO 8536-1, of any size, filled with min. 50 % of the nominal volume of water. Close these 10 infusion bottles with sterilized closures of the type to be tested.

C.3.3 Fix the closures with aluminium caps that meet the requirements of ISO 8536-3.

C.3.4 Place the spike, vertically on the centre of the uncovered part of an unperforated closure as described in [C.2](#).

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 a complete penetration has been achieved, then fix the bottle vertically with the bottom end up, and attach a total mass of $(0,5 \pm 0,025) \text{ kg}$ to the spike. Leave in this position 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 no complete penetration has been achieved, and the number of cases where leakage along the spike during the observation period has occurred.

C.4.2 Report the number of cases where complete penetration has been achieved, and the number where leakage along the spike during the observation period has occurred.

C.4.3 Report the number of cases where the spike was not in place after 4 h under stress.

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Annex D (normative)

Closure piercing device

Since there is no plastic reference spike currently available, the use of the stainless steel spike in [Figure D.1](#) is necessary. The values obtained may not correlate with those obtained with plastic spikes.

Dimensions in millimetres,
Surface roughness values in micrometres

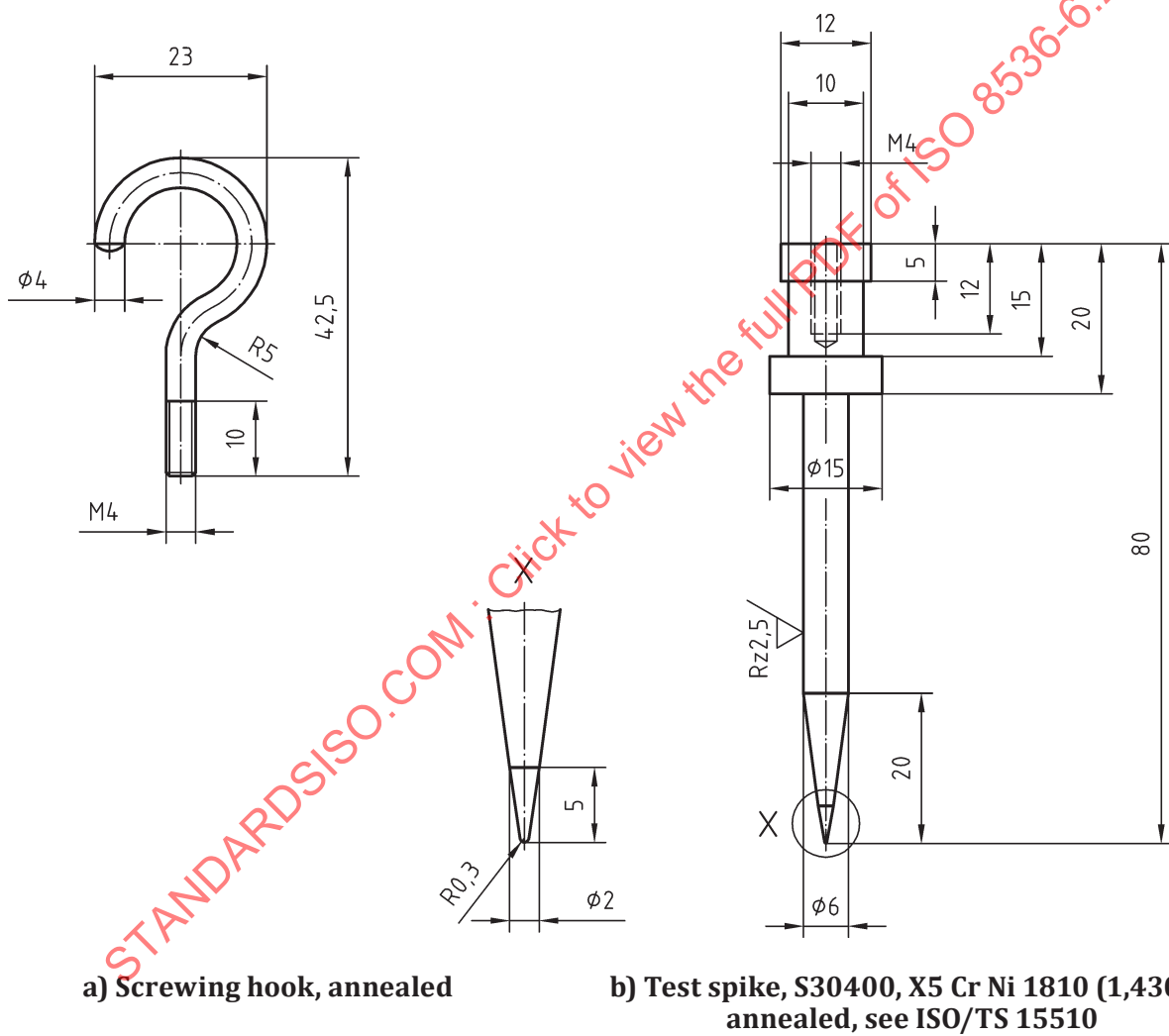


Figure D.1 — Test spike

Annex E (informative)

Determination of residual moisture

E.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.

E.2 Apparatus and materials

E.2.1 Karl-Fischer coulometric device.

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

E.2.3 Nitrogen supply with a molecular sieve cartridge.

NOTE Choose nitrogen with a low moisture content.

E.2.4 Stainless steel weighing boat.

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

E.2.6 Reagents as specified in the measurement system manual.

E.2.7 Sodium tartrate, or equivalent, with known water content (standard).

E.2.8 Control solution 1 % (m/m) water in organic solvent.

E.3 Procedure

E.3.1 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

- low blank drift,
- correct determination of water content of control solution,
- constant slope of the cumulative graph water/time when running a blank, and
- correct determination of water in sodium tartrate.

Daily checking is recommended.