INTERNATIONAL STANDARD

ISO 8536-6

Second edition
2009-11-15

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

Reference number
ISO 8536-6:2009(E)

ISO copyright office
Case postale 56 • CH-1211 Geneva 20
Tel. + 41 22 749 01 11
Fax + 41 22 749 09 47
E-mail copyright@iso.org
Web www.iso.org

Published in Switzerland

Contents

Page

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.

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

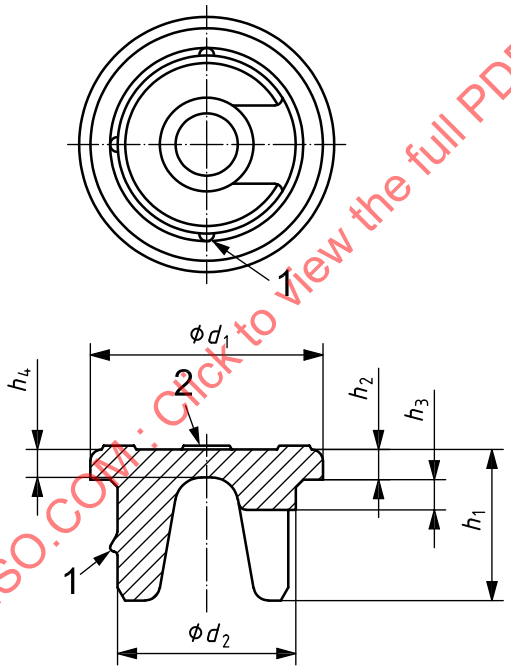
For the purposes of this document, the following terms and definitions apply.

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 ±0,2	d_2[a] ±0,1	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 3302-1 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

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.

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 test system.

If the fragmentation of the reference samples is found to be in the range of known results the testing is recognised 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.

NOTE 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 (A.2.1) 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 (A.2.2) 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 (A.2.4) 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. Ensure that no fragments remain in the bottles. Count and record the number of fragments in the filter visible to 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 using a microscope 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 a certain 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 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 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**, that meets the following requirements:

— 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 to 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 S1 and S2.

B.2.5 **Steam autoclave**, capable of maintaining (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 (B.2.1) 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 (B.2.2) 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 appropriate organic solvent, exerting the utmost care not to blunt it, and clamp spike S1 in the piercing device.

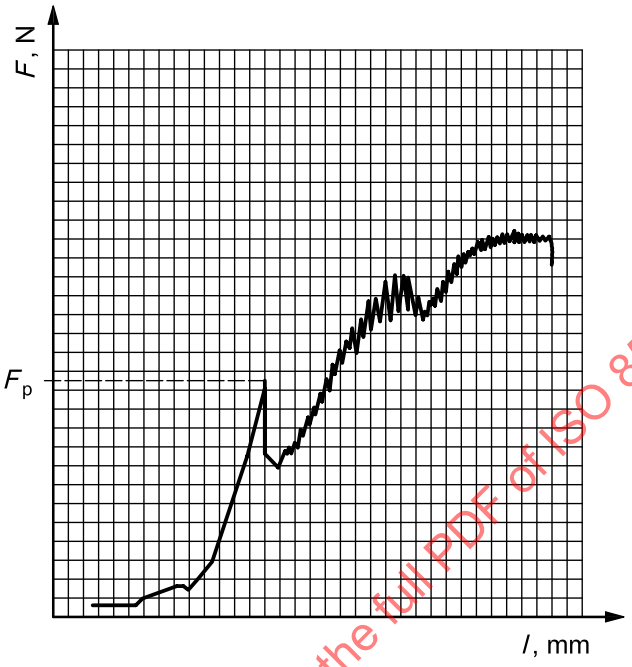
B.3.5 Take the first bottle and remove the tear-off part of the seal so as to have free access to the closure. Place the bottle in the testing device (B.2.3) in such a way that the closure will be perforated perpendicularly and centrally.

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 ten bottles. Calculate the range of the values of penetration force 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 **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 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 (C.2.1) 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 (C.2.2) 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 (C.2.3) 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, then 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 no complete penetration has been achieved, and the number 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.

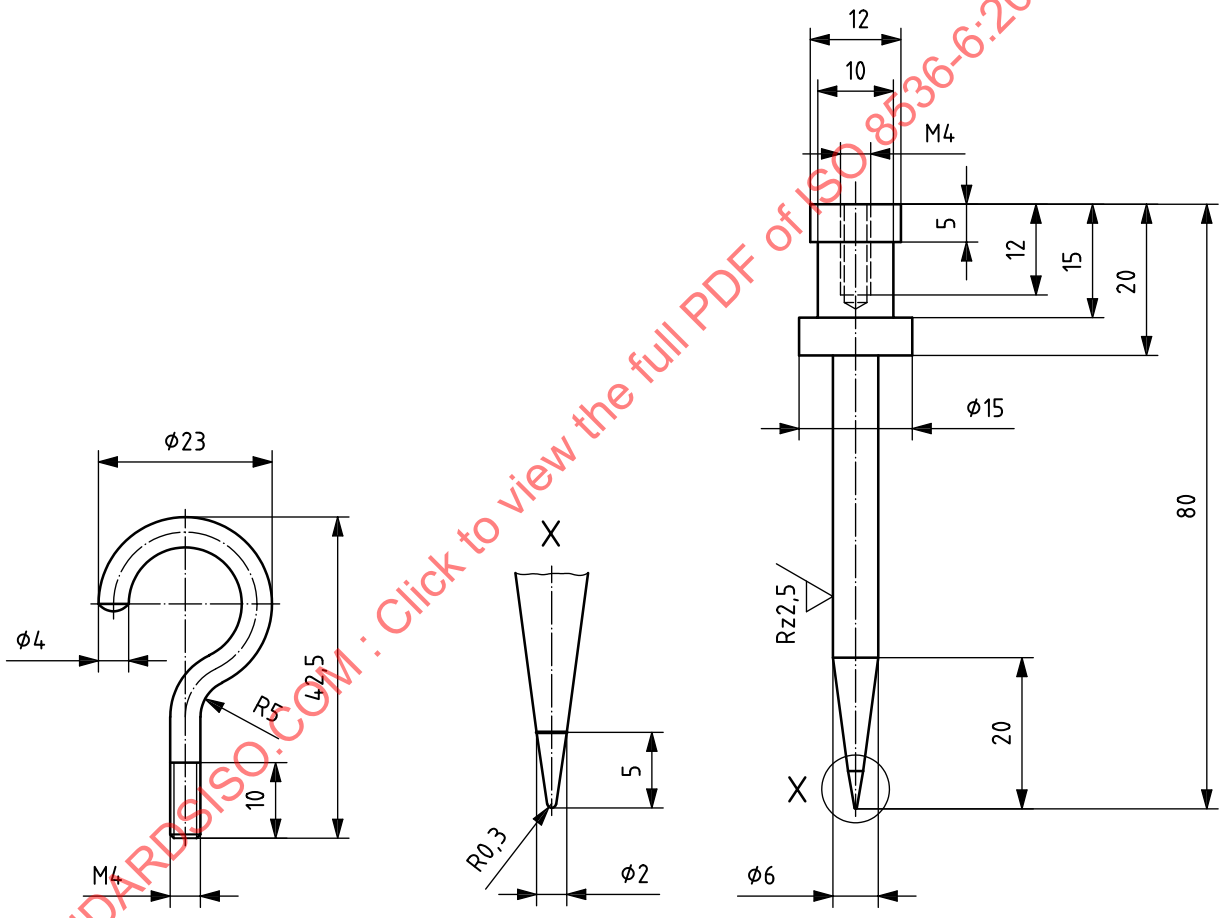
C.4.3 Report the number of cases where the spike was not in place after 4 h under stress.

Annex D
(normative)

Closure piercing device

Since there is no plastic reference spike currently available, the use of the stainless steel spike shown 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



a) Screwing hook, annealed

b) Test spike, S30400, X5 Cr Ni 1810 (1.4301), annealed, see ISO/TS 15510

Figure D.1 — Test spike