INTERNATIONAL STANDARD

ISO 15759

Second edition
2005-04-01

Medical infusion equipment — Plastics caps with inserted elastomeric liner for containers manufactured by the blow–fill–seal (BFS) process

Matériel de perfusion à usage médical — Capsules plastiques avec un joint à base d'élastomère pour récipients produits par le procédé d'extrusion/soufflage/remplissage (ESR)

Reference number
ISO 15759:2005(E)

PDF disclaimer

This PDF file may contain embedded typefaces. In accordance with Adobe's licensing policy, this file may be printed or viewed but shall not be edited unless the typefaces which are embedded are licensed to and installed on the computer performing the editing. In downloading this file, parties accept therein the responsibility of not infringing Adobe's licensing policy. The ISO Central Secretariat accepts no liability in this area.

Adobe is a trademark of Adobe Systems Incorporated.

Details of the software products used to create this PDF file can be found in the General Info relative to the file; the PDF-creation parameters were optimized for printing. Every care has been taken to ensure that the file is suitable for use by ISO member bodies. In the unlikely event that a problem relating to it is found, please inform the Central Secretariat at the address given below.

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 15759 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 15759:2002), which has been technically revised.

Introduction

The materials used to manufacture blow–fill–seal (BFS) containers are primary packaging materials suitable for storing infusion solutions until they are administered. This International Standard deals with plastics caps with inserted elastomeric liners for use with blow–fill–seal containers and describes their dimensional and functional requirements. This International Standard takes into account that the cap is not a primary packaging component.

Medical infusion equipment — Plastics caps with inserted elastomeric liner for containers manufactured by the blow–fill–seal (BFS) process

1 Scope

This International Standard specifies the dimensional and functional requirements for plastics caps with inserted elastomeric liners, attached to the infusion container (BFS container) by welding or by collar technique. These caps are intended for use in the packaging and handling of liquid drugs for parenteral delivery.

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 2230, *Rubber products — Guidelines for storage*

ISO 2768-1, *General tolerances — Part 1: Tolerances for linear and angular dimensions without individual tolerance indications*

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

ISO 7500-1, *Metallic materials — Verification of static uniaxial testing machines — Part 1: Tension/compression testing machines — Verification and calibration of the force-measuring system*

ISO 7864, *Sterile hypodermic needles for single use*

ISO 8871-1, *Elastomeric parts for parenterals and for devices for pharmaceutical use — Part 1: Extractables in aqueous autoclavates*

3 Dimensions and designation

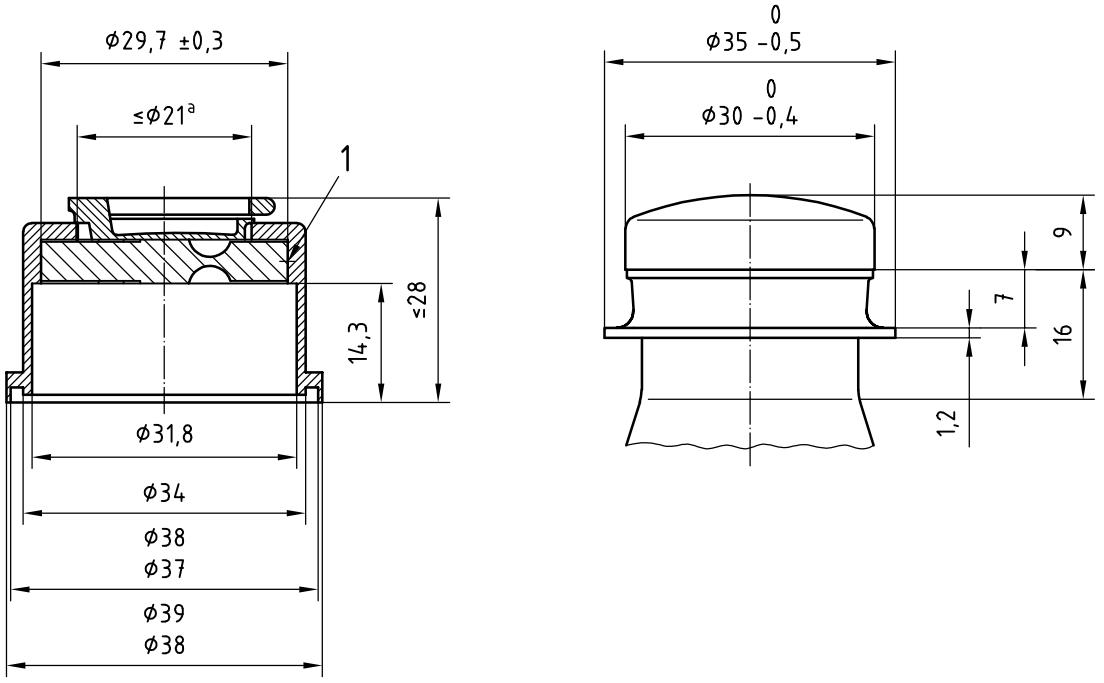
3.1 Plastics cap for attachment by welding technique (Form A)

General tolerances for Form A plastics caps shall be in accordance with ISO 2768-1; dimensions shall be in accordance with Figure 1. Elastomeric liners for such caps shall be in accordance with ISO 3302-1.

Plastics cap(s) of Form A in accordance with this International Standard shall be designated as follows:

Cap ISO 15759-BFS-A

Dimensions in millimetres



Key

1 measuring point at the centre

[a] Diameter of score line.

Figure 1 — Dimensions for Form A plastics caps

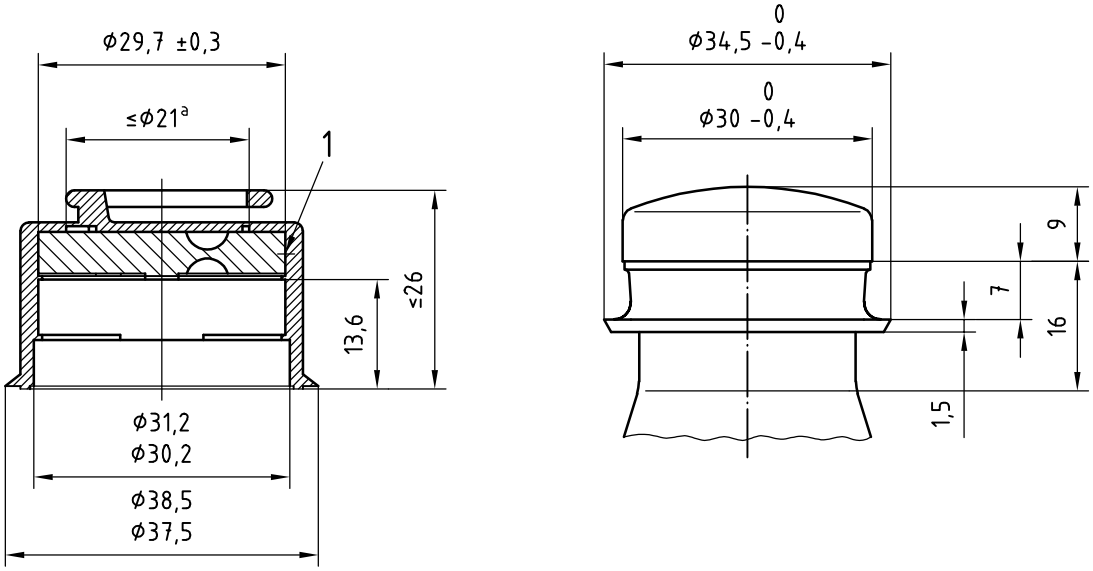
3.2 Plastics cap for attachment by collar technique (Form B)

Dimensions for Form B plastics caps shall be in accordance with Figure 2.

Plastics cap(s) of Form B in accordance with this International Standard shall be designated as follows:

Cap ISO 15759-BFS-B

Dimensions in millimetres



Key

1 measuring point at the centre

[a] Diameter of score line.

Figure 2 — Dimensions for Form B plastics caps

3.3 Elastomeric liner

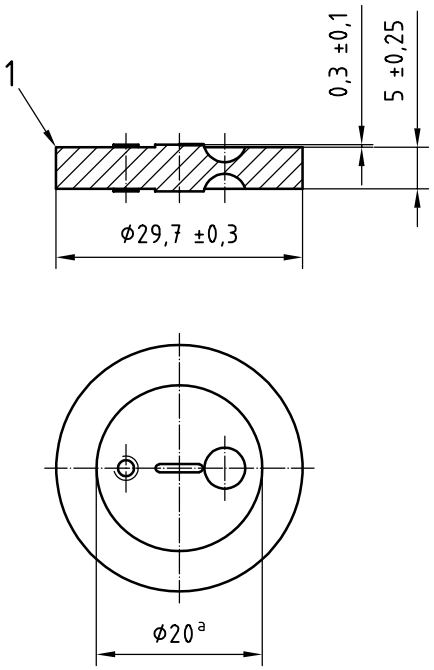
Dimensions for elastomeric liners for plastics caps of Form A or Form B shall be in accordance with Figure 3.

Elastomeric liners in accordance with this International Standard shall be designated as follows:

Elastomeric liner ISO 15759

Figure 3 illustrates a typical liner design. Other liner designs are permitted.

Dimensions in millimetres



Key

1 trimming edge max. ∅ 30,2

[a] Target area.

Figure 3 — Dimensions for elastomeric liners for plastics caps of Form A or Form B

4 Materials for cap and liner

4.1 Materials shall be in accordance with the requirements in Clauses 6, 7, 8 and 9. The choice of plastics and elastomeric materials shall be subject to agreement between manufacturer and customer.

4.2 Resistance to ageing depends largely on pre-sterilization techniques, storage and handling conditions. The period during which cap and liner shall comply with the requirements of this International Standard is subject to agreement between manufacturer and customer.

4.3 Compatibility of the drug with the liner shall be assessed by the user.

4.4 ISO 2230 describes storage guidelines for vulcanized elastomeric parts.

5 Plastics cap — Physical requirements and testing

5.1 Leak-resistance test

When performing the leak-resistance test of the covered piercing area in accordance with Annex A, no leakage shall be observed.

5.2 Opening force

When testing the opening force needed to expose the piercing area in accordance with Annex B, the required force shall not exceed 80 N and shall not tear the cap outside the piercing area.

6 Liner — Physical requirements and testing

6.1 General requirements

6.1.1 Injection gates and sprues are not allowed in the sealing area, i.e. between cap and liner.

6.1.2 Marks, indentations and spacers are allowed. The height of spacers shall not exceed 0,3 mm.

6.2 Hardness

Hardness requirements shall be agreed between manufacturer and customer. The hardness shall not differ from the nominal value by more than when ± 5 IRHD tested in accordance with ISO 48.

6.3 Fragmentation (coring)

When testing for fragmentation in accordance with Annex C, no more than seven fragments of diameter equal to or greater than 50 µm shall be observed per ten piercings.

6.4 Penetration force

When testing for penetration in accordance with Annex D, the force required to penetrate the liner shall not exceed 80 N. The average value shall not exceed 75 N.

6.5 Dynamic spike-retention capability

When tested in accordance with Annex E, the measured retention force shall not fall below 15 N.

6.6 Static spike-retention capability of the liner and leak resistance of the piercing area

When tested in accordance with Annex F, no leakage shall be observed between the spike and liner during a period of 4 h and the spike shall not fall out.

6.7 Resealability

When performing the test in accordance with Annex G, no air shall escape.

7 Plastics cap — Chemical requirements and testing

The plastics material used to manufacture the cap shall be physiologically harmless.

8 Liner — Chemical requirements and testing

The liners shall fulfil the minimum requirements for Type II materials in accordance with ISO 8871-1.

9 Biological requirements for plastics cap and liner

Biological requirements are not part of this International Standard; however, since biological tests are required by most of the national Pharmacopoeia or other health authority regulations, they are mandatory for manufacturers and users in countries where such regulations exist. Where none exist, reference should be made to biological tests, e.g. as described in the United States Pharmacopeia or other pharmacopoeia.

10 Packaging

The packaging shall protect the plastics caps and liners during transportation and storage in such a way that their function is not impaired and they remain clean.

11 Storage

The plastics caps and liners shall be stored as specified in ISO 2230 and shall not be exposed to UV radiation. Under these conditions they shall maintain compliant with the requirements of this International Standard throughout a storage period agreed on between manufacturer and customer.

12 Marking

The packaging of plastics caps and liners, which comply with the requirements of this International Standard, shall be marked as specified in Clause 3, e.g.

Cap ISO 15759-BFS-B

Annex A
(normative)

Leak-resistance test

A.1 Principle

The resistance of the covered piercing area to penetration by surface-active penetrant is determined.

A.2 Reagent

A.2.1 Surface-active penetrant, comprising a mixture of aliphatic hydrocarbons with surface-active substances and colorants.

A.3 Preparation

Autoclave ten liners at sterilization conditions agreed on between manufacturer and customer (typically 106 °C for 50 min or 121 °C for 30 min) and cool down to ambient temperature.

A.4 Procedure

A.4.1 Carefully remove the liners from the ten caps and cover the piercing area with penetrant.

A.4.2 Leave the penetrant on the piercing area for 60 min.

A.4.3 Count the number of samples penetrated by the penetrant.

A.5 Expression of results

Record the number of leak failures.

Annex B
(normative)

Opening force needed to expose the piercing area

B.1 Principle

The force needed to remove the lid of the plastics cap in order to expose the piercing area is determined.

B.2 Apparatus

B.2.1 **Tensile testing machine**, Class 1, in accordance with ISO 7500-1, with a suitable holding device.

B.3 Preparation

Autoclave ten liners at sterilization conditions agreed on between manufacturer and customer (typically 106 °C for 50 min or 121 °C for 30 min) and cool down to ambient temperature.

B.4 Procedure

B.4.1 Fix the cap securely on the tensile testing machine.

B.4.2 Remove the lid axially at a speed of 200 mm/min.

B.4.3 Record the force, with a tolerance of ± 2 N.

B.4.4 Repeat B.4.1 to B.4.3 with the remaining samples.

B.5 Expression of results

Calculate the average from ten measurements.

Indicate the maximum value.

Annex C
(normative)

Fragmentation (coring)

C.1 Principle

Liners to be tested are pierced with a spike. Fragments resulting from piercing the liner are collected and counted in order to assess the relative tendency of the liner to fragment.

C.2 Apparatus

C.2.1 **Holding device**, for liner in accordance with Annex H. Other suitable holding devices may be used provided equivalent results are obtained.

C.2.2 **Spike**, in accordance with Annex I.

C.2.3 **Membrane filter set**.

C.3 Preparation

C.3.1 Autoclave ten liners at sterilization conditions agreed on between manufacturer and customer (typically 106 °C for 50 min or 121 °C for 30 min) and cool down to ambient temperature.

C.4 Procedure

C.4.1 Fill the holding device with distilled water to half its volume. Degrease the spike with acetone and fix it to the piercing device. Place the liner in the holding device.

C.4.2 Pierce the liner manually in the target area, keeping the holding device in a vertical position.

C.4.3 Shake the holding device for several seconds and then withdraw the spike. Open the holding device by removing the liner and empty the contents onto the membrane filter set. Make sure that no fragments remain in the holding device.

C.4.4 Repeat C.4.1 to C.4.3 with the remaining liners.

C.4.5 Count the number of elastomeric fragments using an approved method.

C.5 Expression of results

Report the number of fragments which are equal to or greater than 50 µm after ten liners have been pierced.

Annex D
(normative)

Penetration force

D.1 Principle

The force needed to penetrate the liner with a spike in accordance with Annex I is determined.

D.2 Apparatus

D.2.1 **Holding device**, for liner in accordance with Annex H. Other suitable holding devices may be used provided equivalent results are obtained.

D.2.2 **Spike**, in accordance with Annex I.

D.2.3 **Tensile testing machine**, Class 1, in accordance with ISO 7500-1 with suitable fittings.

D.3 Preparation

Autoclave ten liners at sterilization conditions agreed on between manufacturer and customer (typically 106 °C for 50 min or 121 °C for 30 min) and cool down to ambient temperature.

D.4 Procedure

D.4.1 Degrease the spike with acetone, fix the spike to the fixture of the tensile testing machine and place the liner in the holding device.

D.4.2 Pierce the liner in the target area at a speed of 200 mm/min.

D.4.3 Pierce the liner in the target area at a speed of 200 mm/min until the conical part of the spike has gone through the liner.

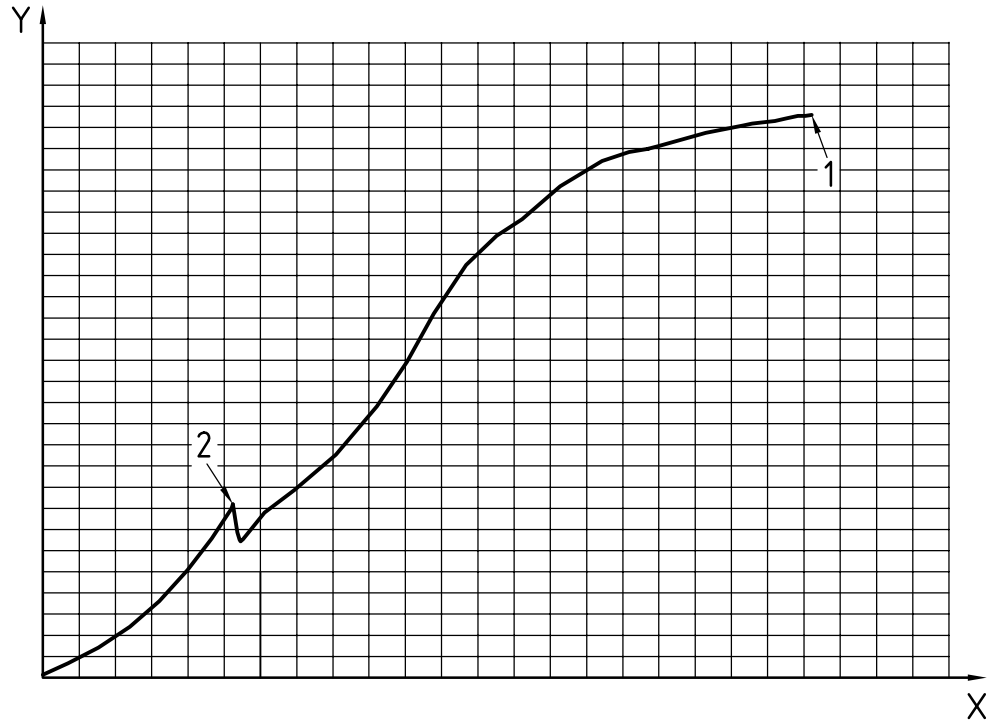
D.4.4 Measure the maximum penetration force, with a tolerance of ± 2 N as indicated in Figure D.1.

D.4.5 Repeat D.4.1 to D.4.4 with the remaining liners.

D.5 Expression of results

D.5.1 Calculate the average value from ten measurements.

D.5.2 Indicate the maximum value of all measurements.



Key

X penetration, mm

Y force, N

1 maximum penetration force

2 piercing force

Figure D.1 — Typical example of a force penetration diagram

Annex E
(normative)

Dynamic spike retention capability

E.1 Principle

The dynamic spike retention capability of the liner is determined using a spike in accordance with Annex I.

E.2 Apparatus

E.2.1 **Holding device**, for liner in accordance with Annex H. Other suitable holding devices may be used provided equivalent results are obtained.

E.2.2 **Spike**, in accordance with Annex I.

E.2.3 **Tensile testing machine**, Class 1, accordance with ISO 7500-1 with suitable fittings.

E.3 Preparation

Autoclave ten liners at sterilization conditions agreed on between manufacturer and customer (typically 106 °C for 50 min or 121 °C for 30 min) and cool down to ambient temperature.

E.4 Procedure

E.4.1 Degrease the spike with acetone and place the liner in the holding device.

If a spike is used according to Annex I, it should be degreased with acetone prior to testing.

E.4.2 Pierce the liner all the way through manually in the target area.

E.4.3 Immediately after piercing, withdraw the spike from the liner at a speed of 200 mm/min using the tensile testing machine.

E.4.4 Measure the maximum force, with a tolerance of $\pm$ 2 N.

E.4.5 Repeat E.4.1 to E.4.4 with the remaining liners.

E.5 Expression of results

E.5.1 Calculate the average value from ten measurements.

E.5.2 Indicate the minimum value of all measurements.

Annex F
(normative)

Static spike-retention capability of the liner and leak resistance of the piercing area

F.1 Principle

The static spike-retention capability of the liner is determined using a spike in accordance with Annex I.

F.2 Apparatus

F.2.1 **Holding device**, for liner in accordance with Annex H. Other suitable holding devices may be used provided equivalent results are obtained.

F.2.2 **Spike**, in accordance with Annex I.

F.2.3 **Weight**, of mass 1 kg.

F.2.4 **Pressurized air**, for subjecting the liner to pressure.

F.3 Preparation

Autoclave ten liners at sterilization conditions agreed on between manufacturer and customer (typically 106 °C for 50 min or 121 °C for 30 min) and cool down to ambient temperature.

F.4 Procedure

F.4.1 Degrease the spike with acetone, fill the liner holding device with water and place the liner in the holding device.

F.4.2 Pierce the liner all the way through manually in the target area.

F.4.3 Place the liner holding device in a vertical position with the liner, facing downwards. Subject the space filled with water to a pressure of 20 kPa (200 mbar). Load the spike with the weight and keep the 1 kg weight in place for 4 h.

F.4.4 Report any leakage between the spike and liner, as well as any changes to the position of the spike during the period specified in F.4.3.

F.4.5 Repeat F.4.1 to F.4.4 with the remaining liners.

F.5 Expression of results

F.5.1 Count the number of leakages from ten liners tested.

F.5.2 Determine the number of times the spike has fallen out.

Annex G
(normative)

Resealability

G.1 Principle

The capability of the liner to reseal after having been pierced with a hypodermic needle is determined.

G.2 Apparatus

G.2.1 **Holding device**, for liner in accordance with Annex H. Other suitable holding devices may be used provided equivalent results are obtained.

G.2.2 **Hypodermic needle**, in accordance with ISO 7864, with an outside diameter of 1,2 mm, bevel type, medium-size.

G.2.3 **Pressurized air**, for subjecting the liner to pressure.

G.3 Preparation

Autoclave ten liners at sterilization conditions agreed on between manufacturer and customer (typically 106 °C for 50 min or 121 °C for 30 min) and cool down to ambient temperature.

G.4 Procedure

G.4.1 Place the liner in the holding device.

G.4.2 Holding the hypodermic needle perpendicular to the liner, pierce the liner target area in three different locations using the same needle.

G.4.3 After the liner has been pierced for the last time, cover the piercing area with water and subject the bottom of the liner to 20 kPa (200 mbar) pressure for 15 s.

G.4.4 Report whether air escapes from the piercing area during the test period of 15 s.

G.4.5 Repeat G.4.1 to G.4.4 with the remaining liners using a new hypodermic needle for each liner.

G.5 Expression of results

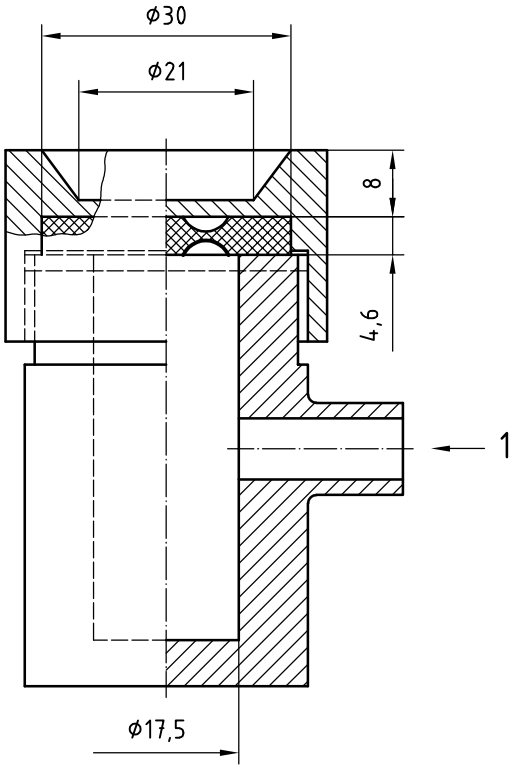
Count the number of liners from which air escapes during the test period.

Annex H
(normative)

Holding device for elastomeric liner

The dimensions of the holding device for the elastomeric liner shall be in accordance with Figure H.1.

Dimensions in millimetres



Key

1 inlet for pressurized air

Figure H.1 — Holding device for elastomeric liner

Annex I
(normative)

Reference spike

The reference spike shall be made of stainless steel and have dimensions in accordance with Figure I.1. It shall be inspected prior to use. It shall be sharp and undamaged. A damaged spike shall be replaced.

NOTE The usage of this type of spike in piercing tests provides results suitable for orientation and comparison purposes. These results may not correlate with results obtained using plastic spikes, such as those specified in ISO 1135-4 or ISO 8536-4, these spikes not having been harmonized with regard to design, material and surface conditions.

Dimensions in millimetres

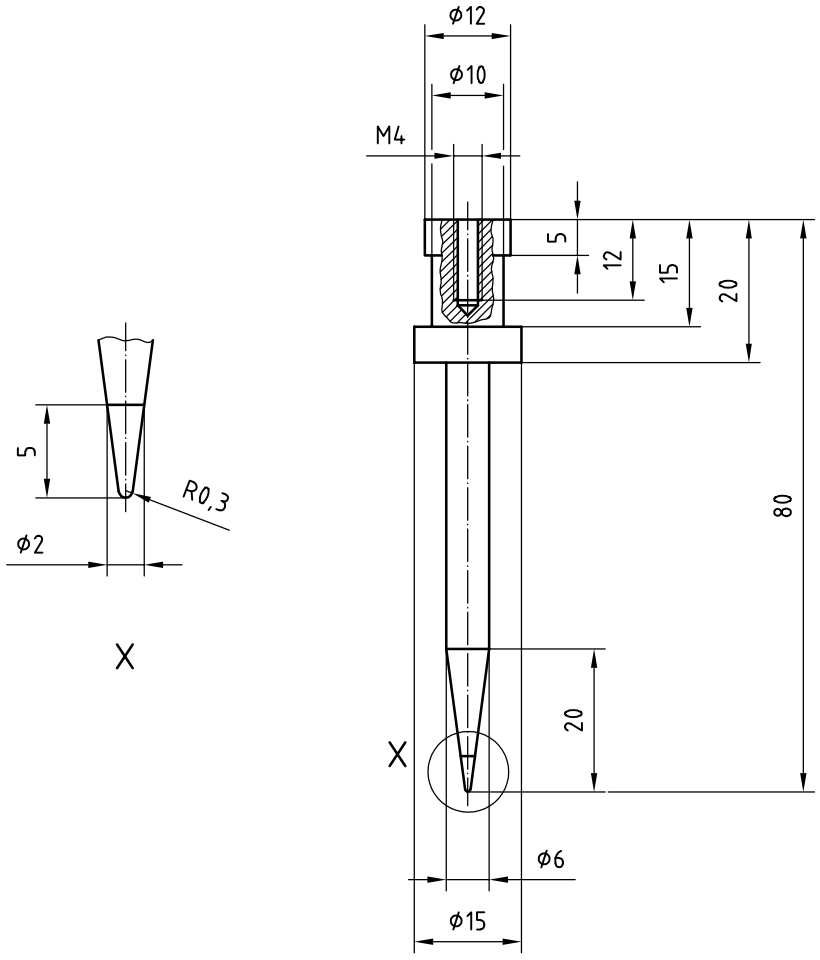


Figure I.1 — Reference spike, annealed

Bibliography

[1] ISO 1135-4, *Transfusion equipment for medical use — Part 4: Transfusion sets for single use*

ICS 11.040.20

Price based on 17 pages