INTERNATIONAL STANDARD

ISO 8536-2

Third edition
2010-03-15

Infusion equipment for medical use —

Part 2:
Closures for infusion bottles

Matériel de perfusion à usage médical —

Partie 2: Bouchons pour flacons de perfusion

Reference number
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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.

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 8536-2 was prepared by Technical Committee ISO/TC 76, *Transfusion, infusion and injection equipment for medical and pharmaceutical use*.

This third edition cancels and replaces the second edition (ISO 8536-2:2001) and ISO 8536:2001/Cor.1:2003 which have 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

The purpose of this part of ISO 8536 is to specify the shape and dimensions of and the requirements for elastomeric closures intended for infusion bottles. In order to provide seal integrity of the container closure systems the dimensions of the elastomeric closures have to be compatible with the dimensions of the infusion bottles and the caps as specified in corresponding parts of ISO 8536.

Primary packaging components made of elastomeric materials are an integral part of medicinal products and thus the principles of current Good Manufacturing Practice (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 2:
Closures for infusion bottles

1 Scope

This part of ISO 8536 specifies the shape, dimensions, material, performance requirements and labelling of closures for infusion bottles as specified in ISO 8536-1.

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 strongly be 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*

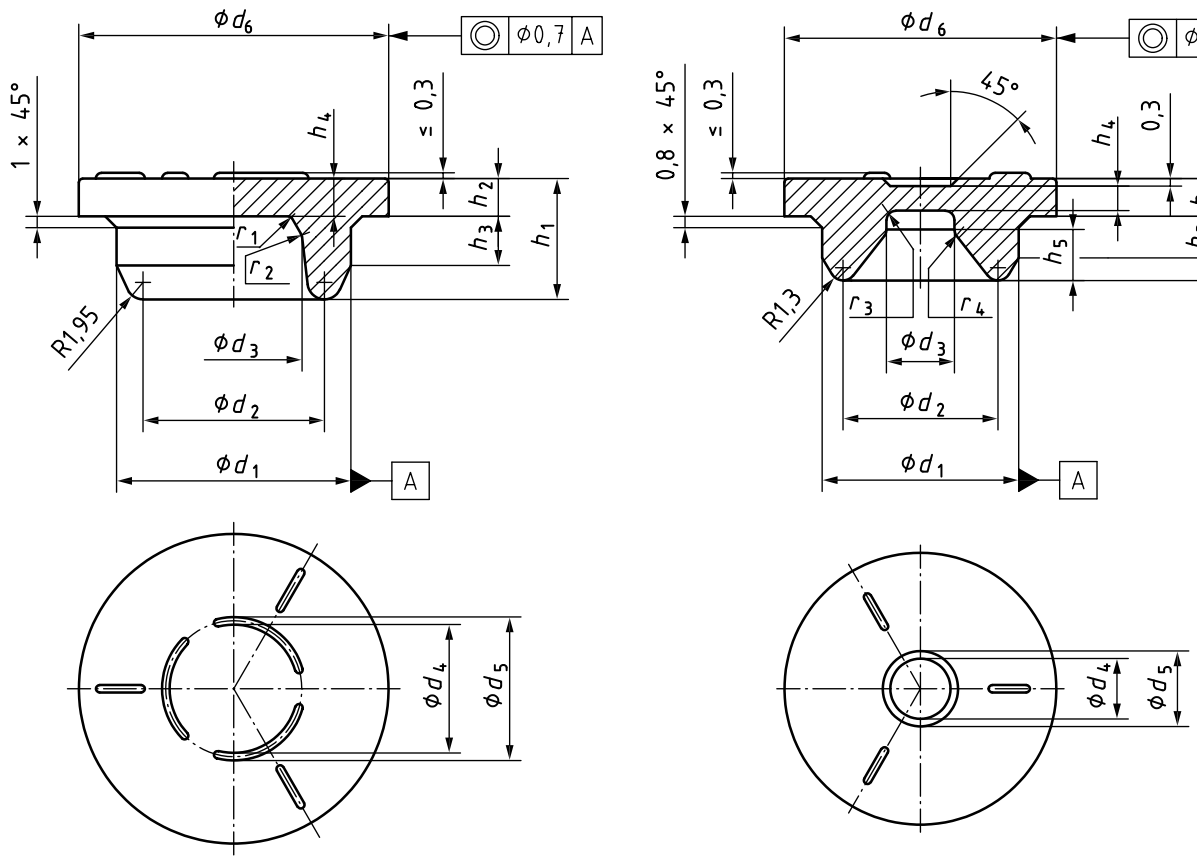
ISO 8871-1, *Elastomeric parts for parenterals and for devices for pharmaceutical use — Part 1: Extractables in aqueous autoclavates*

ISO 8871-4, *Elastomeric parts for parenterals and for devices for pharmaceutical use — Part 4: Biological requirements and test methods*

3 Shape and dimensions

3.1 The shape and dimensions of closures shall be as shown in Figure 1 and as given in Table 1. Figure 1 illustrates two typical designs of closure, types A and B.

Dimensions in millimetres



Type A **Type B**

Figure 1 — Dimensions and configuration of type A and type B closures

Table 1 — Dimensions of infusion closures

Dimensions in millimetres

Type	Nominal size	d_1 ± 0,2	d_2 max.	d_3 min.	d_4 min.	d_5 max.	d_6 ±0,3	h_1 ±0,4	h_2 ±0,3	h_3	h_4[a] ±0,3	h_5
A	32	23,6	18,2	13	13	14	30,8	12,2	4	5,1	4	—
B	28	19,6	15,5	6,9	6,1	7,1	27,1	10,2	3,4	4,2	2,5	5,1

[a] Indentations may reduce the piercing thickness.

3.2 If not otherwise specified, general dimensional tolerances shall be in accordance with ISO 3302-1 and ISO 3302-2.

3.3 In order to facilitate the production process, the flange of the closure may have a slightly conical shape (maximum 0,8 mm related to the diameter). The trimming edge of the flange shall comply with the tolerances specified for the diameter of the flange.

3.4 The diameter, d_4, which defines the piercing area shall not exceed d_3. Marks and indentations may be placed in the piercing area. The height of the marks shall not exceed 0,3 mm.

NOTE The spacers in Figure 1 for type A and type B closures are shown for illustrative purposes only and do not form part of the requirements of this part of ISO 8536.

3.5 All edges of the closure may be rounded.

4 Designation

Closures can be designated according to their type, see Figure 1. The designation is expressed as the number of this part of ISO 8536 followed by the nominal size of the infusion bottle followed by the type letter.

EXAMPLE A type A closure for infusion bottles of nominal size 32 mm complying with the requirements laid down in this part of ISO 8536 is designated as follows:

Infusion closure ISO 8536-2 - 32 - A

5 Material

The elastomeric material used shall meet the requirements specified in Clause 6.

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.

NOTE For use with infusion solutions, resistance to two steam sterilization cycles may not be needed because only terminal sterilization is applied.

Closures shall be made of 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 parameters and compendium requirements.

6 Requirements

6.1 General

The requirements specified in 6.2 to 6.4 represent minimum requirements which refer to the condition of the elastomeric closures on receipt by the user.

6.2 Physical requirements

6.2.1 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 a 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.

6.2.2 Fragmentation

When tested for fragmentation in accordance with Annex A, not more than 20 fragments of diameter ⩾ 50 µm per 10 piercings shall be observed.

6.2.3 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.

6.2.4 Spike retention/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.

6.2.5 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.

6.3 Chemical requirements

The requirements of ISO 8871-1 shall apply.

6.4 Biological requirements

The requirements of ISO 8871-4 shall apply.

7 Labelling

Packed closures which meet the requirements of this part of ISO 8536 can be labelled with the designation given in Clause 4.

Annex A
(normative)

Determination of fragments

A.1 Principle

The purpose of the test is to measure the relative coring tendencies of different ISO 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 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 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 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 with 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 mm 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

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 certain sets 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**, which 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 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 of maintaining a temperature of (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 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 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 an appropriate organic solvent, exerting the utmost care not to blunt it, and clamp spike S1 in the piercing device.

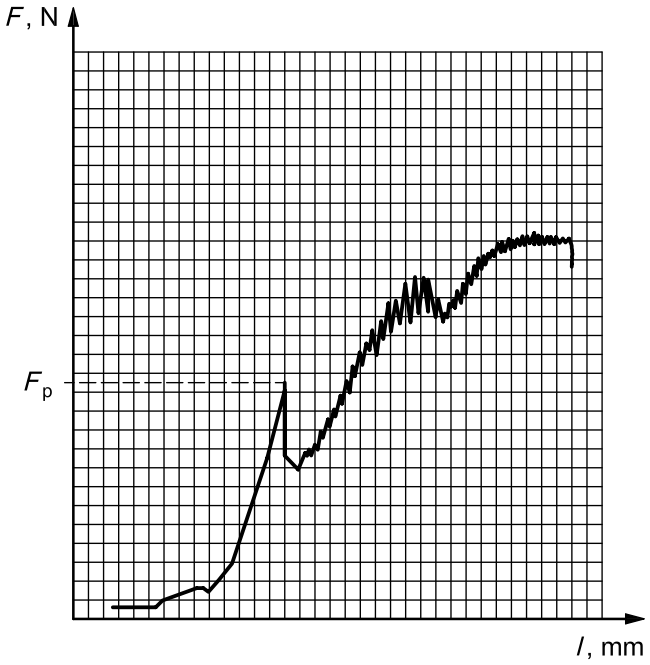
B.3.5 Take the first bottle and remove the tear-off part of the seal so as to have free access to the closure. Place the bottle in the testing device in such a way that the closure will be perforated perpendicularly and centrally.

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, in newtons

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

l movement of the spike, in millimetres

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 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 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, 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, 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.

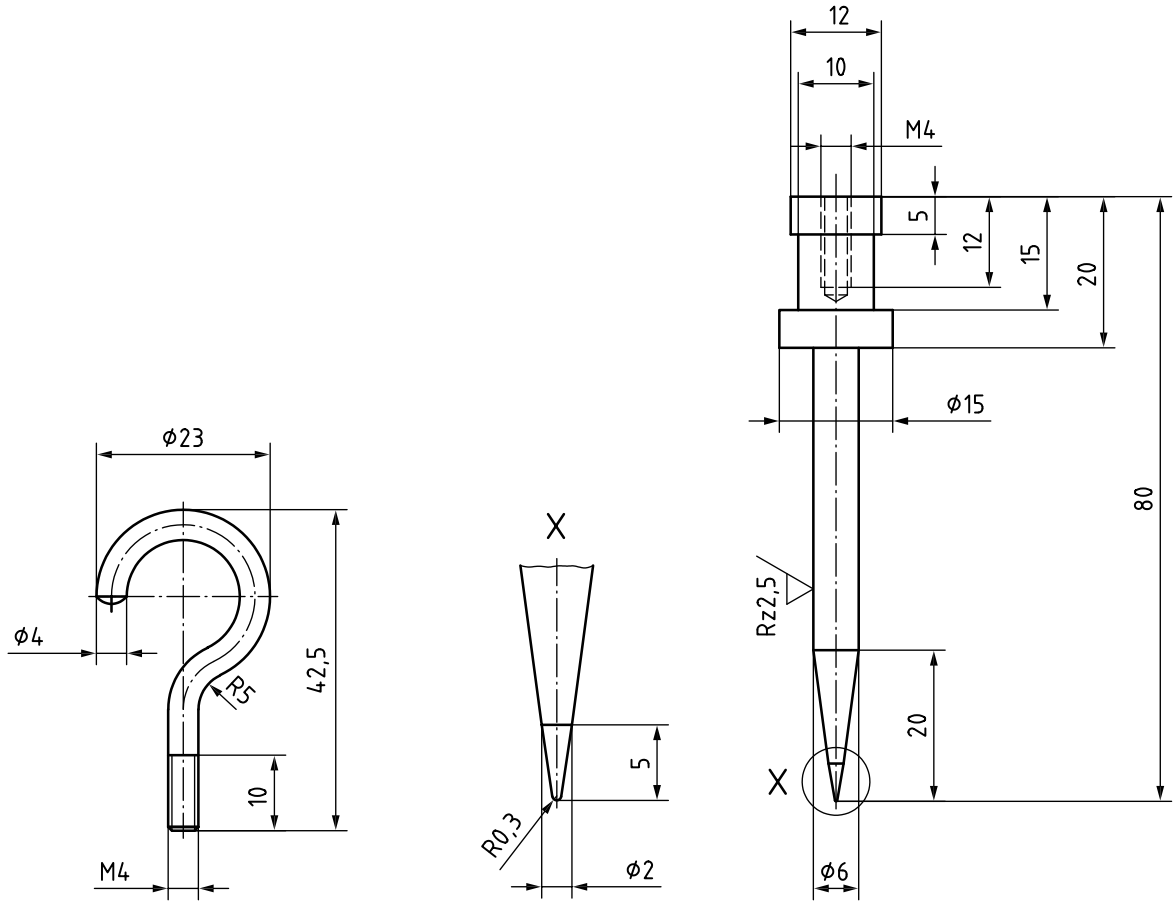
C.4.3 Report the number of cases where the spike was not in place after 4 h under stress.

Annex D
(normative)

Closure piercing device

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

Bibliography

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

[2] ISO 8871-5, *Elastomeric parts for parenterals and for devices for pharmaceutical use — Part 5: Functional requirements and testing*

[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)*

[4] ISO/TS 15510, *Stainless steels — Chemical composition*

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