INTERNATIONAL STANDARD

ISO 8362-5

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Injection containers for injectables 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 8362-5:1995(E)

Contents

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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.

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.

International Standard ISO 8362-5 was prepared by Technical Committee ISO/TC 76, *Transfusion, infusion and injection equipment for medical use*.

ISO 8362 consists of the following parts, under the general title *Injection containers for injectables 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: Injection caps made of aluminium-plastics combinations for injection vials*

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

Annexes A, B, C and D form an integral part of this part of ISO 8362.

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Injection containers for injectables and accessories —

Part 5:

Freeze drying closures for injection vials

1 Scope

This part of ISO 8362 specifies the design, dimensions, material, performance, requirements and test for the type of closure for injections 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.

Closures which form the subject of this part of ISO 8362 are intended for single use only.

2 Normative references

The following standards contain provisions which, through reference in this text, constitute provisions of this part of ISO 8362. At the time of publication, the editions indicated were valid. All standards are subject to revision, and parties to agreements based on this part of ISO 8362 are encouraged to investigate the possibility of applying the most recent editions of the standards indicated below. Members of IEC and ISO maintain registers of currently valid International Standards.

ISO 48:1994, *Rubber, vulcanized or thermoplastic — Determination of hardness (hardness between 10 IRHD and 100 IRHD).*

ISO 3302:1990, *Rubber — Dimensional tolerances for use with products.*

ISO 3696:1987, *Water for analytical laboratory use — Specification and test methods.*

ISO 7864:1993, *Sterile hypodermic needles for single use.*

ISO 7886-1:1993, *Sterile hypodermic syringes for single use — Part 1: Syringes for manuel use.*

ISO 8362-1:1989, *Injection containers for injectables and accessories — Part 1: Injection vials made of glass tubing.*

ISO 8362-2:1988, *Injection containers for injectables and accessories — Part 2: Closures for injection vials.*

ISO 8362-4:1989, *Injection containers for injectables and accessories — Part 4: Injection vials made of moulded glass.*

ISO 8871:1990, *Elastomeric parts for aqueous parenteral preparations.*

3 Definitions

For the purposes of this part of ISO 8362, the following definitions apply.

3.1 freeze drying; lyophilization: Process by which drying is obtained by sublimation of the solvent in the frozen state.

3.2 freeze drying closure: Closure which enables the drying of a frozen good in a vacuum chamber.

It is put in place on top of a glass container after filling, leaving sufficient openings for the sublimation process under vacuum. At the end of the drying process it can be fully inserted into the glass container by hydraulic or mechanical means in the vacuum chamber.

4 Design aspects

4.1 The plug part shall provide slits, channels or other appropriate means in conjunction with protruding or locating elements at the outer diameter, which enable insertion in a drying (halfway) position during the sublimation process.

4.2 The design of the locating element to hold the freeze drying closure firmly in the sublimation position

shall not generate too high a resistance when the closure is fully inserted.

4.3 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, without excessive piercing force and without generating an excessive number of rubber fragments.

4.4 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.

4.5 The freeze drying closure shall be made from the formulation originally tested and approved by the end user.

The manufacturer of the freeze drying closure shall certify identity as well as conformance to previously agreed functional parameters or compendium requirements.

4.6 The design of the freeze drying closure should allow easy cleaning.

4.7 Figure 1 illustrates the general design of a freeze drying closure, the dimensions of which are given in clause 5.

5 Dimensions

5.1 The dimensions of freeze drying closures shall be as given in table 1.

5.2 If not otherwise specified, general dimensional tolerances shall be in accordance with ISO 3302.

5.3 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.

5.4 If the flange of the closure has a slightly conical shape in order to facilitate production, the difference in diameter shall not exceed 0,3 mm for nominal size 13 and 0,6 mm for nominal size 20. The tolerances of the trimmed edge of the flange shall comply with the overall tolerances specified for the flange diameter.

5.5 All edges of the closure may be rounded.

6 Designation

A freeze drying closure for injection vials shall be designated by the words "freeze drying closure", the number of this part of ISO 8362, followed by the nominal size of the closure:

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7 Requirements

7.1 Materials

The elastomeric materials used to manufacture freeze drying closures shall meet the general requirements specified in ISO 8362-2.

NOTE 1 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 transmission.

7.2 Physical requirements and performance

NOTE 2 Requirements for dimensions are specified in clause 5.

7.2.1 Hardness

When tested by the method given in ISO 48 using test plates supplied by the manufacturer, the hardness shall not differ from the value stated by the manufacturer by more than ± 5 IRHD.

7.2.2 Fragmentation (coring)

When tested for fragmentation in accordance with annex A, not more than five fragments per 100 piercings shall be observed.

7.2.3 Penetration force

When tested for penetrability in accordance with annex B, in no case shall a force of more than 10 N be required for penetration of the closure.

7.2.4 Self-sealing

If the closures have to be pierced more than once, but not more than three times, the requirements for self-sealing shall be met. When tested in accordance with annex C, no methylene blue solution shall leak into the interior of the vial.

7.2.5 Closure/container integrity

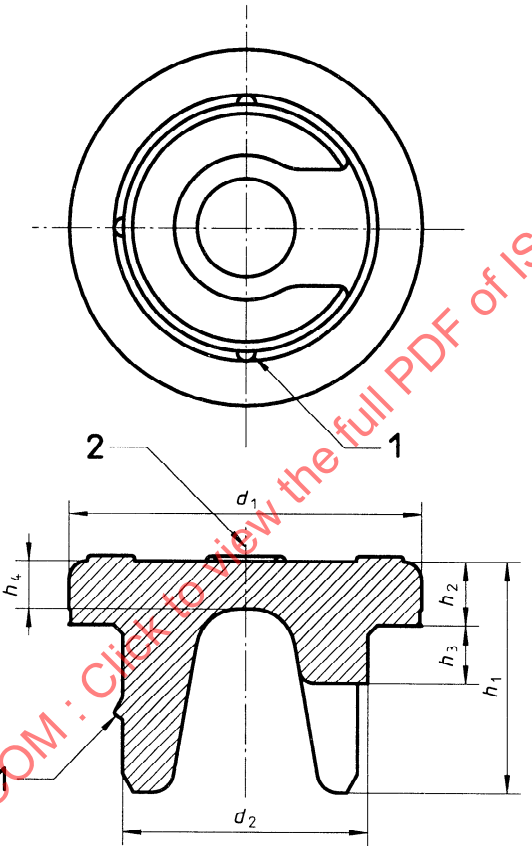
When tested in accordance with annex C, no methylene blue solution shall leak into the interior of the vial.

Table 1 — Dimensions of freeze drying closures

Dimensions in millimetres

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

1) The value of d_2 is applied in that area which is defined by h_3.



1 Locating 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 — Closure example

7.2.6 Resistance to ageing

The minimum shelf life of the closure should be agreed upon between closure manufacturer and user.

NOTES

3 The resistance to ageing depends on the actual circumstances of storage and handling. A guide to storage of vulcanized rubber is laid down in ISO 2230, *Vulcanized rubber — A guide to storage.*

4 The useful lifetime of the closure in contact with the pharmaceutical product is part of the compatibility tests to be carried out by the user.

7.2.7 Mechanical stability of freeze drying closures in evaporation position

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.

7.2.8 Residual moisture

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 a level acceptable for his application.

Annex D describes a method for the determination of residual moisture.

NOTE 5 Freeze drying closures can pick up water during shipping, storage, washing and steam sterilization cycles which it 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.

7.3 Chemical requirements

The chemical limits as specified in table 2 shall be met.

8 Biological requirements

The freeze drying closure shall not release any substances which may adversely affect the therapeutic effectiveness of the injectable products, including those substances which may exhibit toxic, pyrogenic or haemolytic reactions.

Reference shall be made to biological tests, for example as described in the United States Pharmacopoeia, European Pharmacopoeia or other Pharmacopoeias, or related regulations of health authorities.

9 Samples

9.1 Sample size

The closures to be tested shall be taken from a sample collected as specified in ISO 8871.

If not otherwise specified, the following number of samples is needed:

— nominal size 13: 570 pieces
— nominal size 20: 395 pieces

9.2 Sample preparation

Samples for the tests in annexes A, B and C shall be preconditioned as specified by ISO 8362-2:1988, subclause 6.2 and cooled for at least 2 h at room temperature.

10 Labelling

The packaged freeze drying closures shall be labelled in accordance with the designation specified in clause 6.

Table 2 — Chemical limits for freeze drying closures for injection vials

Test	Requirement	Test procedure as described in ISO 8871:1990, annex:
Reducing matter (oxidizables)	≤ 7 ml of $c(KMnO_4)$ = 2 mmol/l per 20 ml	C
Heavy metals (calculated as Pb^{2+})	≤ 10 µg Pb^{2+}/10 ml	D
Ammonium (calculated as NH_4^+)	≤ 20 µg NH_4^+/10 ml	E
Acidity/alkalinity	≤ 1 ml of c(HCl) or c(NaOH) = 5 mmol/l per 20 ml	G
Residue on evaporation (total solids)	≤ 4 mg/100 ml	H
Volatile sulfides (at pH ≈ 2)	coloration of lead acetate paper ≤ 50 µg Na_2S/20 cm^2 rubber surface	J
Zinc (calculated as Zn^{2+})	Zn^{2+} ≤ 30 µg/10 ml	K
Conductivity	≤ 40 µS/cm	L
Turbidity	not exceeding opalescence suspension number 3	M

Annex A
(normative)

Test method for fragmentation

A.1 General

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, design of the sealing head, design of the hypodermic needle point, its sharpness, needle lubrication, needle gauge and the keenness of the operator's sight.

It is, therefore, necessary to control these variables in order to obtain comparable results. For this reason, the closures to be tested shall be compared to known samples.

A.2 Principle

A number of closures is pierced under defined conditions with a suitable hypodermic needle. The closure fragments caused by this operation are collected and counted by visual examination without magnifying aids.

A.3 Apparatus

A.3.1 100 injection vials, complying with ISO 8362-1 or ISO 8362-4.

A.3.2 Hand-operated capping device, and **aluminium caps** with a central hole which fit the injection vials to be used in the test.

A.3.3 Membrane filter set.

A.3.4 Disposable syringe for single use (e.g. as specified in ISO 7886), of 1 ml capacity, fitted with a tip for an injection needle.

A.3.5 10 injection needles, having an outer diameter of 0,8 mm and complying with ISO 7864. The bevel types and dimensions shall be as given in figure A.1 and table A.1; both the long and the medium bevel types are allowed.

Dimensions in millimetres

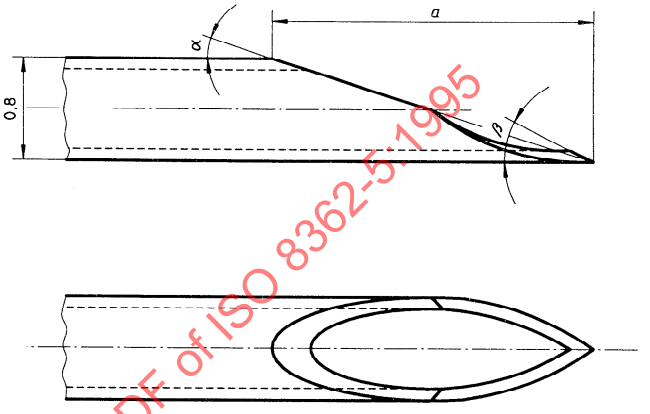


Figure A.1— Needle point

Table A.1 — Bevel dimensions

Bevel type	a mm		α	β
	min.	max.	nom.	
L (long)	3,21	3,78	13°	22° ± 1°
M (medium)	2,70	3,09	15° 30′	26° ± 1°

A.4 Procedure

A.4.1 Degrease 10 new injection needles (A.3.5) by means of acetone or methyl isobutyl ketone.

A.4.2 Select 100 vials (A.3.1) in a size matching the closure, preconditioned according to 9.2.

Place n ml of water in each of these vials, where n is 50 % of the nominal volume of the vials.

Place a closure of the type to be tested on each of 50 vials, and a closure with known fragmentation properties on each of the remaining 50 vials.

Seal all vials with an aluminium cap (A.3.2) using the hand-operated capping device.

Arrange the vials in two rows as shown in figure A.2.

A.4.3 Attach an injection needle (A.3.5) to the tip of the syringe (A.3.4) (see, however, A.4.8). Fill the syringe with water. Remove any water adhering to the needle.

A.4.4 Hold the syringe vertically by hand and pierce closure No. 1 within the marked area, leaving vial No. 1 standing firmly in a vertical position.

Withdraw the needle.

A.4.5 Repeat all of the procedure described in A.4.3 and A.4.4. However, before withdrawing the needle for the last time, inject the contents of the syringe (1 ml of water) into the vial.

A.4.6 Repeat the procedure described in A.4.3 to A.4.5, using closure No. 51 fitted on vial No. 51 (i.e. the first closure/vial combination in the second row).

A.4.7 Repeat all of the procedures described in A.4.3 to A.4.6, using, alternately, vials from the two rows, until all of the closures have each been pierced twice.

A.4.8 Use a new injection needle after every 20 piercings (see figure A.2).

A.4.9 Remove the closures to be tested from the vials (first row). Put the contents of all of them through one membrane filter. Ensure that no fragments remain in the vials. Count and record the number of fragments on the filter visible with the naked eye under normal conditions at a distance between eye and filter of 25 cm.

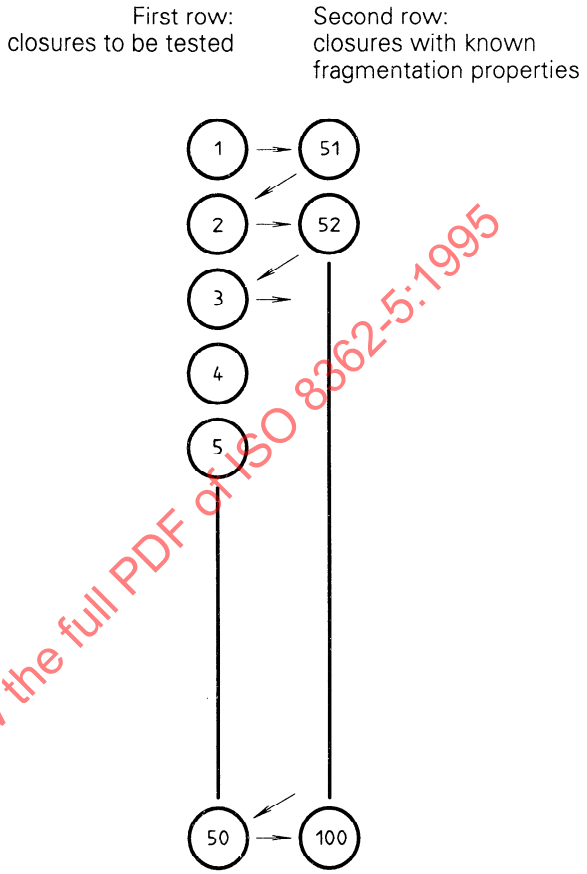
A.4.10 Repeat the procedure described in A.4.9, using, however, the vials with closures having known fragmentation properties.

A.5 Expression of results

The recorded numbers of fragments per 100 piercings for the two series shall be reported.

A.6 Validity

The results obtained on the test closures shall be considered invalid if the results on the known closures lack consistency.



Needle No.[1]	Closure/vial combination No.
1	1; 51; 2; 52; 3; 53; 4; 54; 5; 55
2	6; 56; 7; 57; 8; 58; 9; 59; 10; 60
3	11; 61; 12; 62; 13; 63; 14; 64; 15; 65
etc.	etc.

1) Each needle is used for 20 piercings only (see A.4.8).

Figure A.2 — Test sequence for fragmentation test

Annex B
(normative)

Test method for penetrability

B.1 Principle

Measurement of the force needed to penetrate a closure with a hypodermic needle of 0,8 mm diameter.

B.2 Apparatus

B.2.1 10 injection vials, complying with ISO 8362-1 and matching the closures to be tested, as follows.

Nominal size of closure	Vial
13	4 R/6 ml
20	6 R/10 ml

B.2.2 Hand-operated capping device and **aluminium caps** with a central hole which fit injection vials to be used in the test.

B.2.3 10 injection needles, having an outer diameter of 0,8 mm and complying with ISO 7864; the bevel type and dimensions shall be as specified for the long (L) type in A.3.5 and table A.1.

B.2.4 Piercing device, for instance as shown in figure B.1, possessing a shaft assembly capable of moving vertically upward and downward, and allowing loading with a known vertical force. As an alternative a suitably adapted weighing scale, capacity at least 1 kg, may be used.

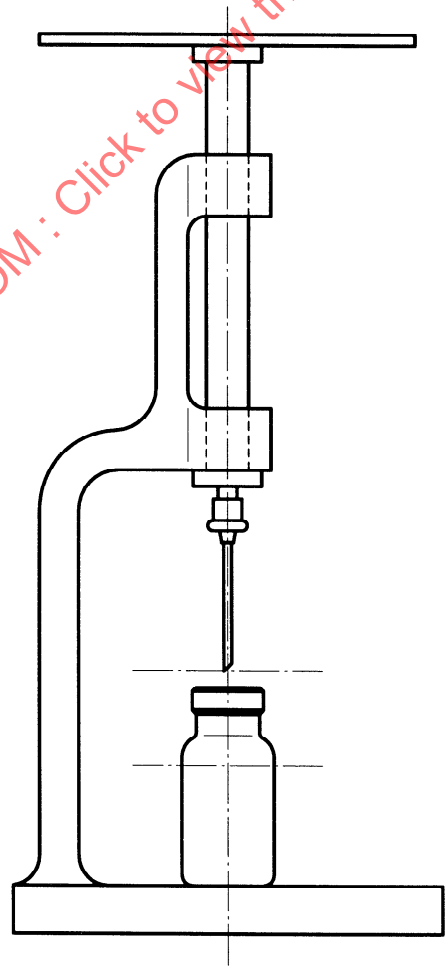


Figure B.1 — Schematic representation of device for testing penetrability

B.3 Procedure

B.3.1 Close 10 test vials with the preconditioned closures according to 9.2. Seal the vials with the appropriate aluminium caps.

B.3.2 Choose between B.3.2.1 and B.3.2.2.

B.3.2.1 Place an assembly in the piercing device (figure B.1), equipped with a new injection needle.

Place a total mass of 1 kg on the injection needle in such a way that a force of 10 N is not exceeded.

Note the result as "pass" if within 15 s the needle has penetrated the closure.

Repeat with the next vial and the next needle until a total of 10 vials has been tested.

B.3.2.2 (Alternative method) Place an assembly in theadapted weighing apparatus, equipped with a new injection needle.

Increase the force on the needle stepwise, in such a way that a force of 10 N is not exceeded.

Note the force at which penetration occurs.

Repeat with the next vial and the next needle, until a total of 10 vials has been tested.

B.4 Expression of results

Report the number of cases in which penetration occurred at a force below 10 N.