INTERNATIONAL STANDARD

ISO 8362-2

First edition
1988-12-15

INTERNATIONAL ORGANIZATION FOR STANDARDIZATION
ORGANISATION INTERNATIONALE DE NORMALISATION
МЕЖДУНАРОДНАЯ ОРГАНИЗАЦИЯ ПО СТАНДАРТИЗАЦИИ

Injection containers for injectables and accessories —

Part 2 :
Closures for injection vials

Récipients et accessoires pour produits injectables —

Partie 2 : Bouchons pour flacons

Reference number
ISO 8362-2 : 1988 (E)

Contents

Printed in Switzerland

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 approval before their acceptance as International Standards by the ISO Council. They are approved in accordance with ISO procedures requiring at least 75 % approval by the member bodies voting.

International Standard ISO 8362-2 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*

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

Introduction

The materials from which injection containers (including the elastomeric closures) are made are suitable primary packaging materials for storing injectable products until they are administered.

Injection containers for injectables and accessories —

Part 2 :
Closures for injection vials

1 Scope

This part of ISO 8362 specifies the design, dimensions, material, performance, requirements and tests for closures for injection vials covered by ISO 8362-1 and ISO 8362-4.

Closures specified in this part of ISO 8362 are intended for single use only.

The closure shall be made from the formulation originally tested and approved by the end-user. The closure manufacturer will certify identity of the closure as well as conformance of the closure to previously agreed functional parameters or compendium requirements.

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 listed below. Members of IEC and ISO maintain registers of currently valid International Standards.

ISO 48 : 1979, *Vulcanized rubbers — Determination of hardness (Hardness between 30 and 85 IRHD).*

ISO 2859 : 1974, *Sampling procedures and tables for inspection by attributes.*

ISO 3302 : 1976, *Rubber — Dimensional tolerances of solid moulded and extruded products.*

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

ISO 7864 : 1984, *Sterile hypodermic needles for single use.*

ISO 7886 : 1984, *Sterile hypodermic syringes for single use.*

ISO 8362-1 : 1988, *Injection containers for injectables and accessories — Part 1: Injection vials made of glass tubing.*

ISO 8362-4 : 1988, *Injection containers for injectables and accessories — Part 4: Injection vials made of moulded glass.*

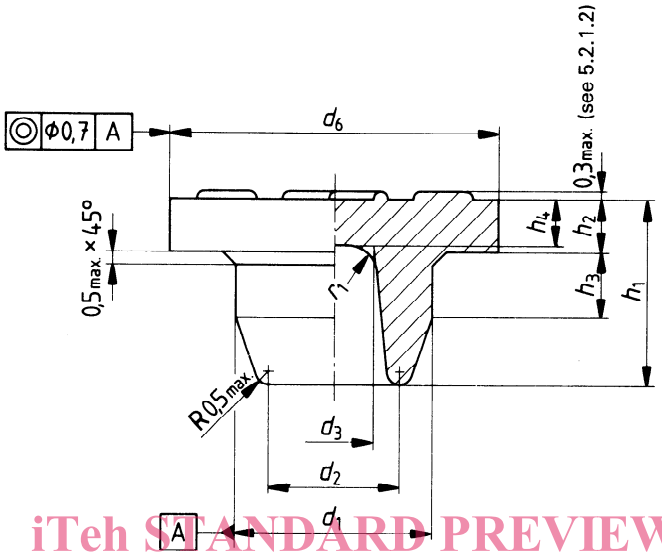
ISO 8871 : 1988, *Elastomeric parts for aqueous parenteral preparations — Identification, requirements, test methods.*

3 Dimensions and designation

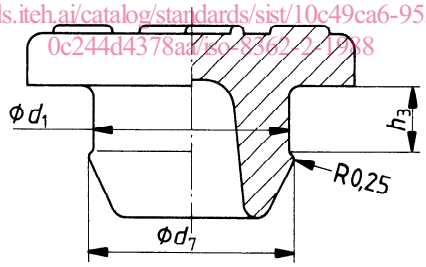
3.1 Dimensions

The dimensions of closures shall be as shown in figure 1 and as given in table 1. Figure 1 illustrates two types of closure, types A and B.

Dimensions in millimetres



Type A



NOTE — Other dimensions are as indicated for type A closures.

Type B

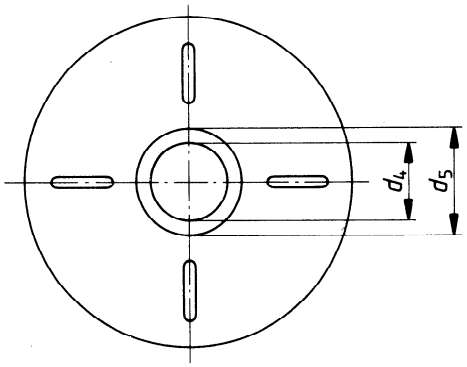


Figure 1 — Dimensions and configuration of types A and B closures

Table 1 — Dimensions of injection closures

Dimensions in millimetres

Type	Nominal size	d_1 ±0,1	d_2 max.	$d_3 = d_4$ min.	d_5 max.	d_6 ±0,2	d_7 ±0,2	h_1 ±0,3	h_2 ±0,25	h_3 ±0,25	h_4	r_1	Injection vials	
													ISO 8362-1	ISO 8362-4
A	13	7,5	5	3	4	12,5	—	7	2	2,5	1,75 ± 0,25	1	2 R and 4 R	—
	20	13,2	10	4,5	5,5	18,8	—	8,8	3,3	2,5	3,3 max. 1,5 min.	2	6 R to 30 R	5 H to 100 H
B	13	7,4	5	3	4	12,5	7,6	7	2	1,5	1,5 min.	1	—	2 I to 10 I
	20	13	10	4,5	5,5	18,8	13,3	8,8	3,3	1,5	3,3 max. 1,5 min.	2	—	5 H to 100 H

3.2 Designation

Closures are designated according to type: the two types A and B are illustrated in figure 1. The designation is expressed as the number of this part of ISO 8362 followed by the nominal size of the vial followed by the type letter.

For example a type A closure for injection vials of nominal size 13 complying with the requirements laid down in this part of ISO 8362 is designated:

Injection closure ISO 8362-2 - 13 - A

4 Material

The type of elastomeric material used shall meet the requirements specified in clause 5.

5 Requirements

5.1 General

The requirements specified in 5.2 to 5.4 represent minimum requirements which refer to the condition of the elastomeric closures on receipt by the user.

NOTE — The resistance to ageing depends on the actual circumstances of storage and handling. The minimum shelf life of the closure should be agreed upon between closure manufacturer and user.

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.

5.2 Physical requirements and performance

5.2.1 Dimensions

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

5.2.1.2 If spacers are located on top of the flange, they shall not interfere with the marks for the injection site within the area of diameter d_5 (see figure 1). The height of the spacers shall not exceed 0,3 mm.

NOTE — The spacers in figure 1 for types A and B closures are shown for illustrative purposes only and do not form part of the requirements of this part of ISO 8362.

5.2.1.3 If the flange of the closure has a slightly conical shape, it shall be 0,3 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 of the flange d_6.

5.2.1.4 All edges of the closure may be rounded.

5.2.2 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.

5.2.3 Fragmentation (coring)

When tested for fragmentation in accordance with annex A, not more than 5 fragments per 100 piercings shall be observed.

5.2.4 Penetration

When tested for penetration in accordance with annex B, the force needed to penetrate the closure shall not exceed 10 N for any of the ten closures tested.

5.2.5 Closure/container integrity

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

5.2.6 Self-sealing

If the closure has 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.

5.3 Chemical requirements

The material of the closure shall satisfy the limits specified in table 2.

Table 2 — Chemical limits for injection closures

Characteristics	Limit	Test method as described in ISO 8871
Reducing matter (oxidizables)	≤7,0 ml of $c(KMnO_4)$ = 2 mmol/l per 20 ml	Annex C
Heavy metals (calculated as Pb^{2+})	≤10 µg Pb^{2+}/10 ml	Annex D
Ammonium (calculated as NH_4^+)	≤20 µg NH_4^+/10 ml	Annex E
Acidity/ alkalinity	≤1,0 ml of c(HCl) or c(NaOH) = 5 mmol/l per 20 ml	Annex G
Residue on evaporation (total solids)	≤ 4 mg/100 ml	Annex H
Volatile sulfides (at ≈ pH 2)	Discoloration of lead acetate paper ≤50 µg Na_2S/20 cm^2 of rubber surface	Annex I
Zinc (calculated as Zn^{2+})	Zn^{2+} ≤ 30 µg/10 ml	Annex K
Conductivity	≤40 µS/cm	Annex L
Turbidity	Not exceeding 3	Annex M

5.4 Biological requirements

The elastomeric 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.

NOTE — Since biological tests are usually requested by most of the national Pharmacopoeias or related regulations of health authorities, they are mandatory for producers and users in countries where they exist.

If this is not the case, reference should be made to biological tests, e.g. as described in the United States Pharmacopoeia, European Pharmacopoeia or other Pharmacopoeias.

6 Sample

6.1 Sample size

The closures to be tested shall be taken from a sample collected as described in ISO 8871; the sample size is deduced from the rules given in ISO 2859.

The minimum sample size to produce a sufficient number of items for all physical and chemical tests is as follows:

— nominal size 13 : 570 closures;

— nominal size 20 : 395 closures.

6.2 Pre-conditioning for physical properties testing

Pre-condition the samples for fragmentation, penetrability and integrity and self-sealing as follows.

Estimate the total surface area, A, in square centimetres, of the quantity of closures to be treated. Wash the closures by placing them in a suitable glass container and covering with ($2A$) ml of purified water[1]. Boil the water for 5 min ± 15 s, and rinse 5 times with cold purified water. Place the washed closures in a wide-necked flask and add ($2A$) ml of purified water. Cover the mouth of the flask with aluminium foil or a borosilicate beaker. Heat in an autoclave so that a temperature of 121 °C ± 1 °C is reached in the flask within 30 min; maintain this temperature for 30 min.

Allow the closures to cool to room temperature within 30 min. Dry the closures in hot air at 60 °C within 60 min. Store the closures in a closed glass container.

7 Marking

The packaging closures given shall be marked with the designation given in 3.2.

1) Purified water corresponds to grades 1 and 2 of ISO 3696.

Annex A
(normative)

Test method for fragmentation

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 hypodermic needle point, its sharpness, the amount of lubrication on the needle, the gauge of the needle 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 have to be compared to known samples.

A.2 Apparatus

A.2.1 50 injection vials, complying with ISO 8362-1 or ISO 8362-4.

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

A.2.3 Membrane filter set.

A.2.4 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.2.5 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 type are allowed.

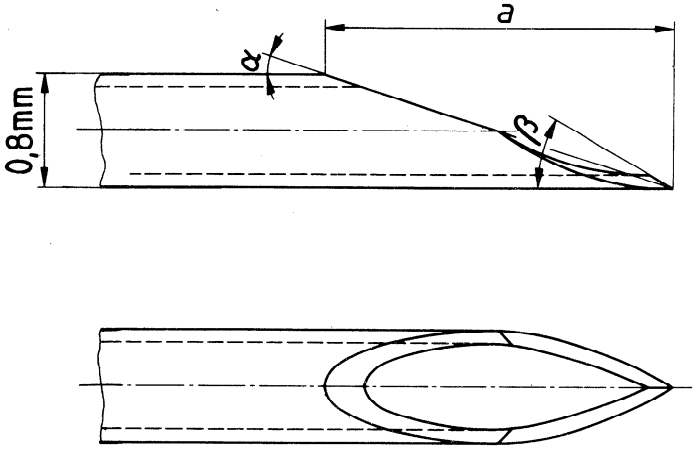


Figure A.1 — Needle point

Table A.1 — Dimensions of bevel

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.3 Procedure

A.3.1 Degrease 10 new injection needles (A.2.5) by means of acetone or methyl-isobutylketone.

A.3.2 Select 50 vials (A.2.1) in a size matching the closure to be tested.

Place n ml of water into 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 25 vials, and a closure with known fragmentation properties on each of the remaining 25 vials.

Seal all vials with an aluminium cap (A.2.2) using the hand-operated capping device.

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

A.3.3 Attach an injection needle (A.2.5) to the tip of the syringe (A.2.4) (see, however, A.3.8). Fill the syringe with water. Remove any water adhering to the needle.

A.3.4 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.3.5 Repeat the procedure described in A.3.4 three more times; however, before withdrawing the needle for the last time, inject the contents of the syringe (1 ml of water) into the vial.

A.3.6 Repeat the procedures described in A.3.3 to A.3.5, using closure No. 26 fitted on vial No. 26 (i.e. the first closure/vial combination in the second row).

A.3.7 Repeat all of the procedures described in A.3.3 to A.3.6, using, alternately, vials from the two rows, until all of the closures have each been pierced four times.