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Elastomeric parts for parenterals and for devices for pharmaceutical use —

Part 5: Functional requirements and testing

Éléments en élastomère pour administration parentérale et dispositifs à usage pharmaceutique —

Partie 5: Exigences fonctionnelles et essais

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Foreword

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The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

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For an explanation on the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the WTO principles in the Technical Barriers to Trade (TBT) see the following URL: Foreword - Supplementary information

The committee responsible for this document is ISO/TC 76, *Transfusion, infusion and injection, and blood processing equipment for medical and pharmaceutical use*.

This second edition cancels and replaces the first edition (ISO 8871-5:2005), which has been technically revised.

ISO 8871 consists of the following parts, under the general title *Elastomeric parts for parenterals and for devices for pharmaceutical use*:

— *Part 1: Extractables in aqueous autoclavates*

— *Part 2: Identification and characterization*

— *Part 3: Determination of released-particle count*

— *Part 4: Biological requirements and test methods*

— *Part 5: Functional requirements and testing*

Introduction

Elastomeric or rubber closures for pharmaceutical use are used in combination with vials and many times in conjunction with piercing devices. There are three functional parameters which are important to the piercing process. These are penetrability, fragmentation and self-sealing. The three functional tests described in this part of ISO 8871 can be used as a reference method for testing elastomeric closures that are pierced using injection needles made from metal. In addition, the aqueous solution tightness test can be used to verify the effectiveness of the sealing of a specific closure/vial combination.

Elastomeric parts for parenterals and for devices for pharmaceutical use —

Part 5:
Functional requirements and testing

1 Scope

This part of ISO 8871 specifies requirements and test methods for functional parameters of elastomeric closures used in combination with vials and when pierced by an injection needle.

NOTE Functional testing with spikes is specified in ISO 8536-2 and in ISO 8536-6.

2 Normative references

The following documents, in whole or in part, are normatively referenced in this document and are indispensable for its application. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 7864, *Sterile hypodermic needles for single use*

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

ISO 8362-3, *Injection containers and accessories — Part 3: Aluminium caps for injection vials*

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

ISO 8362-6, *Injection containers and accessories — Part 6: Caps made of aluminium-plastics combinations for injection vials*

3 Terms and definitions

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

3.1
penetrability
force required for piercing an elastomeric closure

3.2
fragmentation
measure of the number of elastomeric particles which are generated by the piercing process

3.3
self-sealing
measure of the resealing efficiency of elastomeric closures following penetration and withdrawal of a needle

3.4
aqueous solution tightness
measure for the effective sealing of a specific elastomeric closure/vial combination

4 Requirements

4.1 Penetrability

When tested in accordance with Annex A, the force required for piercing shall not be greater than 10 N for each closure.

4.2 Fragmentation

When tested in accordance with Annex B, the number of elastomeric fragments per 48 piercings visible with the naked eye shall not be greater than 5.

4.3 Self-sealing and aqueous solution tightness

When tested in accordance with Annex C, none of the vials shall contain any trace of coloured solution when observed with the naked eye. This requirement applies to multi-dose containers only, i.e. containers which utilize elastomeric closures that are pierced multiple times.

Materials that meet the requirements are not required to undergo further testing in accordance with 4.4.

4.4 Aqueous solution tightness

When tested in accordance with Annex D, none of the vials shall contain any trace of coloured solution when observed with the naked eye.

5 Preparation of elastomeric closures for testing

5.1 Sampling

The number of closures required for each test is as follows.

— Penetrability: 10

— Fragmentation: 12

— Self-sealing and aqueous solution tightness: 10

— Aqueous solution tightness: 10

In practice, it is recommended that more than the minimum required number of closures be prepared for testing.

5.2 Cleaning

Closures shall be sterilized in the as-delivered condition. If samples from regular production cleaning processes are not available, the stoppers shall be cleaned in accordance with the following procedure.

Introduce an appropriate number of rubber closures in a suitable glass container, cover with particle-free water, boil for 5 min, then rinse five times with cold particle-free water.

5.3 Sterilization

The closures shall be tested after having been subjected to the sterilization method actually used.

Annex A
(normative)

Test for penetrability

A.1 General

Many elastomeric closures for pharmaceutical use are used in conjunction with injection needles. The force necessary to penetrate or pierce a rubber closure is an important parameter in evaluating the suitability of the closure for its intended use.

A.2 Principle

The force necessary to completely pierce an elastomeric closure is measured using a suitable apparatus.

A.3 Apparatus, equipment and reagents

A.3.1 **10 closures**, prepared in accordance with Clause 5.

A.3.2 **10 clean vials**, in accordance with ISO 8362-1 or ISO 8362-4, neck finish size to match the size of closures (A.3.1) (e.g. 13 mm, 20 mm).

A.3.3 **10 aluminium or plastic/aluminium crimp seals**, in accordance with ISO 8362-3 or ISO 8362-6, sized to match the size of closures (A.3.1) (e.g. 13 mm, 20 mm), and crimping apparatus.

A.3.4 **10 lubricated long-bevel** [bevel angle (11 ± 2)°] **metal hypodermic needles**, external diameter of 0,8 mm in accordance with ISO 7864.

A.3.5 **Apparatus**, capable of measuring a force of 10 N with an accuracy of ±0,25 N.

A.4 Procedure

A.4.1 Close the vials (A.3.2) with the closures (A.3.1) to be tested and secure with a crimp seal (A.3.3).

A.4.2 Fit the force-measuring apparatus (A.3.5) with a hypodermic needle (A.3.4) and pierce a closure perpendicular to the surface. Record the maximum force. Use a new needle for each of the 9 remaining closures and repeat the procedure.

A.5 Expression of results

Record the force required for piercing each closure and compare the test results with the requirement in 4.1.

Annex B
(normative)

Test for fragmentation

B.1 General

Many elastomeric closures for pharmaceutical use are used in conjunction with injection needles. Elastomeric fragments may be released upon penetration with these injection needles. The number and size of these fragments can affect the quality of drug products with which the elastomeric closures are used.

B.2 Principle

Elastomeric closures for injection vials are pierced with an injection needle. Elastomeric fragments which have been caused by piercing are collected on a filter and counted.

B.3 Apparatus, equipment and reagents

B.3.1 **12 closures**, prepared in accordance with Clause 5.

B.3.2 **12 clean vials**, in accordance with ISO 8362-1 or ISO 8362-4, neck finish size to match the size of closures (B.3.1) (e.g. 13 mm, 20 mm).

B.3.3 **12 aluminium or plastic/aluminium crimp seals**, in accordance with ISO 8362-3 or ISO 8362-6, size to match the size of closures (B.3.1) (e.g. 13 mm, 20 mm), and crimping apparatus.

B.3.4 **Particle-free water**, to fit the fill volumes of the vials (B.3.2) and syringe (B.3.6).

B.3.5 **12 lubricated long-bevel** [bevel angle (11 ± 2)°] **metal hypodermic needles**, external diameter of 0,8 mm in accordance with ISO 7864.

B.3.6 **Syringe**, capable of being fitted with the needles in B.3.5.

B.3.7 **Filter**, with a pore size of 0,5 µm.

B.3.8 **Filtering apparatus**, capable of holding a filter (B.3.7) with a pore size of 0,5 µm.

B.3.9 **Laboratory microscope or a magnification glass**, with a minimum magnification of 6.

B.4 Procedure

B.4.1 Place in each of the 12 clean vials (B.3.2) a volume of particle-free water (B.3.4) equivalent to the nominal volume minus 4 ml (e.g. place 21 ml in a 25 ml vial). Close the vials with the closures (B.3.1) to be tested and secure with a crimp seal (B.3.3).

B.4.2 Pierce each closure using a hypodermic needle (B.3.5) fitted to a clean syringe (B.3.6) filled with particle-free water (B.3.4), and inject into the vial 1 ml of water and remove 1 ml of air. Carry out this

operation four times for each closure, piercing each time at a different site. Use a new needle for each closure and check that the needle is not blunted during the test.

B.4.3 Pass the liquid from each of the 12 vials through a filter (B.3.7) having a pore size of 0,5 µm and count the number of particles visible with the naked eye. The count is based on the assumption that fragments with a diameter equal to or greater than 50 µm are visible with the naked eye. In cases of doubt or dispute, count the rubber fragments with a microscope or magnifying glass (B.3.9) to verify their size and nature.

B.5 Expression of results

Record the total number of fragments and compare to the limit given in 4.2.

Annex C
(normative)

Test for self-sealing and dye solution tightness

C.1 General

Elastomeric closures for pharmaceutical use are commonly used in conjunction with vials. The closure ensures an appropriate seal with the vial. Poor closure/vial seal integrity and/or poor self-sealing can affect the sterility of the vial contents, product volume and concentration of doses.

Many elastomeric closures for pharmaceutical use are used in conjunction with injection needles. For multiple-dose containers, the closures may be pierced many times over the course of delivering all the doses. Self-sealing or reseal of the incision made by the needle is important to the container integrity.

C.2 Principle

Elastomeric closures for injection vials are pierced several times with an injection needle and examined for leakage forced by a pressure differential across the closure.

C.3 Apparatus, equipment and reagents

C.3.1 **10 closures**, prepared in accordance with Clause 5.

C.3.2 **10 clean vials**, in accordance with ISO 8362-1 or ISO 8362-4, neck finish size to match the size of closures (C.3.1) (e.g. 13 mm, 20 mm).

C.3.3 **10 aluminium or plastic/aluminium crimp seals**, in accordance with ISO 8362-3 or ISO 8362-6, size to match the size of closures (C.3.1) (e.g. 13 mm, 20 mm), and crimping apparatus.

C.3.4 **Particle-free water**, to fit the fill volumes of the vials (C.3.2).

C.3.5 **Solution of methylene blue**, 1 g/l.

NOTE The presence of surfactants can change the leaking behaviour of a liquid, and therefore, it is advisable to avoid it.

C.3.6 **10 lubricated long-bevel** [bevel angle (11 ± 2)°] **metal hypodermic needles**, external diameter of 0,8 mm in accordance with ISO 7864.

C.3.7 **Vacuum chamber**, capable of maintaining a pressure (27 kPa below atmospheric pressure) for 10 min.

C.4 Procedure

C.4.1 Place in each of the 10 clean vials (C.3.2) a volume of particle-free water (C.3.4) equivalent to the nominal volume (e.g. place 25 ml in a 25 ml vial). Close the vials with the closures (C.3.1) to be tested and secure with a crimp seal (C.3.3).

C.4.2 Using a new hypodermic needle (C.3.6) for each closure, pierce each closure 10 times, piercing each time at a different site within the target area. Immerse the vials upright in a container holding the solution of methylene blue (C.3.5). Ensure that the vials are completely immersed in the solution. Place the container of vials in a vacuum chamber (C.3.7) and reduce the pressure by 27 kPa. Hold the vacuum for 10 min, then restore to atmospheric pressure. Allow the vials to remain immersed in the methylene blue solution for an additional 30 min, then remove them from the chamber. Rinse the outside of the vials with water. Inspect the vial contents visually for any traces of the blue-coloured solution of methylene blue.

C.5 Expression of results

Report if the vials contain any trace of coloured solution and compare to the requirements in 4.3.

Annex D
(normative)

Test for dye solution tightness

D.1 General

Elastomeric closures for pharmaceutical use are commonly used in conjunction with vials. The closure ensures an appropriate seal with the vial. Poor closure/vial seal integrity can affect the sterility of the vial contents, product volume and concentration of doses.

D.2 Principle

Vials that are filled with liquid, stoppered and capped are submerged in a coloured solution. The vials are inspected for leakage as a result of a pressure differential across the closure/vial interface.

D.3 Apparatus, equipment and reagents

D.3.1 **10 closures**, prepared in accordance with Clause 5.

D.3.2 **10 clean vials**, in accordance with ISO 8362-1 or ISO 8362-4, neck finish size to match the size of closures (e.g. 13 mm, 20 mm).

D.3.3 **10 aluminium or plastic/aluminium crimp seals**, in accordance with ISO 8362-3 or ISO 8362-6, size to match the size of closures (e.g. 13 mm, 20 mm), and crimping apparatus.

D.3.4 **Particle-free water**, to fit the fill volumes of the vials.

D.3.5 **Solution of methylene blue**, 1 g/l.

D.3.6 **Vacuum chamber**, capable of maintaining a pressure of 27 kPa below atmospheric pressure for 10 min.

D.4 Procedure

D.4.1 Place in each of the 10 clean vials (D.3.2) a volume of particle-free water (D.3.4) equivalent to the nominal volume (e.g. place 25 ml in a 25 ml vial). Close the vials with the closures (D.3.1) to be tested and secure with a crimp seal (D.3.3).

D.4.2 Immerse the vials upright in a container holding the solution of methylene blue (D.3.5). Ensure that the vials are completely immersed in the solution. Place the container of vials in a vacuum chamber (D.3.6) and reduce the pressure by 27 kPa. Hold the vacuum for 10 min, then restore to atmospheric pressure. Allow the vials to remain immersed in the methylene blue solution for an additional 30 min, then remove them from the chamber. Rinse the outside of the vials with water. Inspect the vial contents visually for any traces of the blue-coloured solution of methylene blue.