INTERNATIONAL STANDARD

ISO 21882

First edition
2019-10

Sterile packaged ready for filling glass vials

Flacons en verre préremplissables sous emballage stérile

Reference number
ISO 21882:2019(E)

ISO copyright office
CP 401 • Ch. de Blandonnet 8
CH-1214 Vernier, Geneva
Phone: +41 22 749 01 11
Fax: +41 22 749 09 47
Email: copyright@iso.org
Website: 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.

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).

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. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT), see www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 76, *Transfusion, infusion and injection, and blood processing equipment for medical and pharmaceutical use*.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

In the last few years, following the more and more urgent request for ready for filling containers, packaging manufacturers managed to offer to the pharmaceutical industry containers already washed and sterilized. This category of products was born about 30 years ago with the appearance on the market of ready for filling syringes.

Only recently, the sterilized sub-assembled ready for filling syringes have been standardized by ISO 11040-4 and ISO 11040-7, including the corresponding packaging system. These two International Standards define the performance requirements of the glass syringes and the related test methods, as well as the ready for filling packaging system for these syringes, also including the test methods.

ISO 8362-1 specifies the form, dimensions and capacities of bulkware glass vials.

Due to the increasing market presence of syringes ready for filling and the associated advantages of this product for the pharmaceutical industry, the suppliers of packaging materials started to develop systems of this type for vials.

The availability of two packaging configurations makes ready for filling glass vials suitable to be used both in clinical trials and in mass production. Nest and tub configuration has been conceived to be used usually with automated filling machines, while tray configuration is usually suitable for small batches filled manually or by means of semi-automated filling machines.

This duality of packaging configurations calls for a standardization of the production processes, materials quality and analytical methods when launching these products on the market, in order to avoid conceiving too highly customized processes.

Sterile packaged ready for filling glass vials

1 Scope

This document specifies the characteristics of sterile and ready for filling empty glass vials for injectable preparations, including the minimum requirements of materials, packaging systems and analytical test methods.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements 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 720, *Glass — Hydrolytic resistance of glass grains at 121 °C — Method of test and classification*

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

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

ISO 10993-7, *Biological evaluation of medical devices — Part 7: Ethylene oxide sterilization residuals*

ISO 11138 (all parts), *Sterilization of health care products — Biological indicators*

ISO 11140 (all parts), *Sterilization of health care products — Chemical indicators*

ISO 11607-1, *Packaging for terminally sterilized medical devices — Part 1: Requirements for materials, sterile barrier systems and packaging systems*

3 Terms and definitions

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

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at http://www.electropedia.org/

3.1
customer
business entity which purchases sterilized ready for filling vials and conducts further processing or filling as appropriate

3.2
filling volume
90 % of the brimful capacity

[SOURCE: United States Pharmacopoeia Convention, USP <660>]

3.3
insert liner
foil to cover and protect the vials

3.4
manufacturer
business entity which performs or is otherwise responsible for the manufacturing of the vials ready to be filled by the *customer* (3.1)

3.5
nest
plastic plate with a defined hole pattern for the placing of the vials

[SOURCE: ISO 11040-7:2015, 3.4, modified — "suspension of the syringe bodies" was replaced with "placing of the vials".]

3.6
packaging system
combination of the *sterile barrier system* (3.10) and *protective packaging* (3.7)

[SOURCE: ISO 11139:2018, 3.192]

3.7
protective packaging
configuration of materials designed to prevent damage to the *sterile barrier system* (3.10) and its contents from the time of their assembly until the point of use

[SOURCE: ISO 11139:2018, 3.219]

3.8
protective bag
plastic bag or sealing around the *tub* (3.12) or the *tray* (3.11)

[SOURCE: ISO 11040-7:2015, 3.6, modified — "tray" was added as an additional configuration.]

3.9
sealing lid
microbial barrier material for sealing the *tub* (3.12) or the *tray* (3.11)

[SOURCE: ISO 11040-7:2015, 3.7, modified — "tray" was added as an additional configuration.]

3.10
sterile barrier system
minimum package that prevents ingress of microorganisms and allows aseptic presentation of product at the point of use

3.11
tray
plastic container with optional supports to accommodate individual vials

3.12
tub
plastic container to accommodate the filled *nest* (3.5)

[SOURCE: ISO 11040-7:2015, 3.11]

4 Quality system

4.1 General

The testing hereunder described shall be carried out within a formal quality system.

NOTE ISO 15378 contains requirements for a suitable quality management system for primary packaging materials for medicinal products.

4.2 Testing

4.2.1 Any suitable test system can be used, when the required accuracy (calibration) and precision (gauge repeatability and reproducibility) can be obtained. In case the gauge is applied, repeatability and reproducibility of the test apparatus shall be no greater than the range documented in test method precision and bias statements or as established by industry round robin studies.

4.2.2 The sampling plans used for the selection and testing of sterile ready for filling vials or components thereof shall be based upon statistically valid rationale at all process steps.

NOTE Examples of suitable sampling plans are given in ISO 2859-1 and ISO 3951 (all parts).

4.2.3 Unless agreed otherwise, testing shall be performed at ambient laboratory conditions.

5 Process description and requirements

5.1 Washing

5.1.1 Washing is the process intended to reduce particle, lubricant or any other contamination on the bulkware vials after converting process steps.

5.1.2 Water used for final rinsing shall meet the specifications of water for injection (WFI) (see USP and/or Ph.Eur).

5.2 Drying

Drying is an optional step to guarantee the absence of rinsing water after washing if heating is not applied. The air shall be filtered using a filter with a pore size of maximum 0,22 µm.

5.3 Packaging

5.3.1 Non-sterile glass vials, already washed, shall be packed in plastic trays or nest and tub configuration as agreed between the manufacturer and the customer. See Annex F.

5.3.2 For packaging systems for sterilized ready for filling vials, see Clause 7.

5.4 Sterilization

5.4.1 Sterilized ready for filling vials shall be sterilized according to a sterility assurance level (SAL) of 10^{-6}, using a suitable validated sterilization method (see, e.g. ISO 11135, ISO 17665-1, ISO 11137 (all parts) or ISO 14937).

5.4.2 The sterilization process shall not compromise the product safety and performance. Sterilization compatibility of sterile barrier systems and packaging systems is assessed following the requirements in ISO 11607-1.

NOTE Sterility testing is subject to national or regional pharmacopoeias, see the methods given in Ph. Eur., 2.6.1, USP <71> and JP 4.06.

For ethylene oxide sterilization the requirements for residuals of ISO 10993-7 apply. See also Reference [21].

6 Requirements for glassware

6.1 General

Vials shall be produced from glass with characteristics such as to be adequate to contain products for injection.

6.2 Material

6.2.1 The material shall be colourless (cl) or amber (br) glass of the hydrolytic resistance grain class HGA 1 in accordance with ISO 720.

6.2.2 Material requirements for hydrolytic resistance shall conform with ISO 8362-1 or ISO 8362-4. For additional requirements, see the requirements for glass type I given in Ph. Eur. 3.2.1, USP <660> and in JP 7.01.

6.3 Dimensions

The dimensions of injection vials made of glass tubing should meet the requirements of ISO 8362-1:2018, Figure 1 or Figure 2 or Figure 3, as appropriate, and Table 1, or ISO 8362-4:2011, Figure 1 or Figure 2, as appropriate, and Table 1 or Table 2, as appropriate. Dimension of vials for different applications not included in ISO 8362-1 or ISO 8362-4 can be acceptable if agreed upon with the customer.

6.4 Particles

6.4.1 Visible particles

Sterilized vials ready for filling shall be manufactured by processes that reduce the risk of particulate contamination.

NOTE Current pharmacopoeias identify visible particulates in injectables as undesirable, but they do not define the size or put a limit on the allowable number for primary packaging material. The manufacturer and the customer can agree upon the size and number of visible particles and the test method.

6.4.2 Sub-visible particles

The particle-related specifications given in pharmacopoeias (e.g. Ph. Eur., USP, JP) do not apply to empty containers but apply to final filled product. For sample preparation for particulate determination, see Annex E.

NOTE 1 See also Ph. Eur. 2.9.19, Ph. Eur. 2.9.20, USP <788>, JP 6.06 and JP 6.07.

For sub-visible particles, the following limits apply for empty containers:

a) if determined by using the light obscuration particle count test (see USP <788> Method 1):

   — particles ≥ 10 µm: 600 max. per container;

   — particles ≥ 25 µm: 60 max. per container.

b) if determined by using the microscopic particle count test (see USP <788> Method 2):

   — particles ≥ 10 µm: 300 max. per container;

   — particles ≥ 25 µm: 30 max. per container.

NOTE 2 These limits are the 10 % of the USP <788> (small volume parenteral) limit values for filled containers with a nominal volume of less than 100 ml (Test 1.B and Test 2.B).

6.5 Bacterial endotoxin level

6.5.1 For bacterial endotoxins, the limit value for vials shall be < 0,25 EU/ml considering the filling volume. For sample preparation for endotoxin determination, see Annex E.

6.5.2 The vials ready for filling shall be processed to remove pyrogens to ensure that they are suitable for their intended use. Such processes shall be validated for three log endotoxin reduction.

NOTE For rationale, see USP monograph on sterile water for injection, see USP <1231>. For testing, see Ph. Eur., 2.6.14, method c), USP <85> and JP 4.01.

7 Requirements for packaging system

7.1 General

7.1.1 The packaging system intended to contain the ready for filling vials shall protect the vials and their sterile barrier system during handling, distribution and storage, in order to maintain the sterility and the functional and cosmetic characteristics over the claimed shelf-life.

NOTE Functional but also cosmetic defects determine a non-conforming product.

7.1.2 The materials, the sterile barrier system, and the packaging system that enable sterilization, protect the product and maintain sterility until the point of aseptic filling shall be in accordance with the requirements of ISO 11607-1.

7.1.3 The packaging system shall have acceptable microbiological and particulate levels to support the introduction of the sterilized vials into an aseptic filling environment and related designated cleanrooms.

NOTE The introduction of sterilized packaged vials into an aseptic filling environment poses a risk of microbiological and/or particulate contamination of the drug product.

7.1.4 Requirements should be agreed upon by the manufacturer and the customer.

7.1.5 Tubs, nests, lids, inserts, trays and protective bags shall allow general processing and aseptic presentation of sterilized vials over their shelf-life. The process steps to be considered include, but are not limited, to the following:

a) for tubs and trays including sealing lid and insert liner:
   1) lid sealing and lid opening;
   2) conveying;
   3) nest/tray insertion and extraction;
   4) stacking and destacking;
   5) sterilization and decontamination.

b) for nests:
   1) container insertion (nesting) and extraction (denesting);
   2) filling;
   3) stoppering;
   4) lyophilization;