
**Sterile packaged ready for filling glass
cartridges**

Cartouches en verre préremplissables sous emballage stérile

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Contents

	Page
Foreword	iv
Introduction	v
1 Scope	1
2 Normative references	1
3 Terms and definitions	1
4 Quality system	3
4.1 General	3
4.2 Testing	3
5 Process description and requirements	3
5.1 Washing	3
5.2 Drying	3
5.3 Lubrication	3
5.4 Capping and crimping	4
5.5 Plunger insertion	4
5.6 Packaging	4
5.7 Sterilization	4
6 Requirements for glassware	4
6.1 General	4
6.2 Material	4
6.3 Dimensions	5
6.4 Particles	5
6.4.1 Visible particles	5
6.4.2 Sub-visible particles	5
6.5 Bacterial endotoxin level	5
7 Requirements for packaging system	6
7.1 General	6
7.2 Nest and tub configuration	7
7.3 Tray configuration	7
7.4 Nest	7
7.5 Tub and tray	8
7.6 Insert liner	8
7.7 Sealing lid	8
7.8 Protective bag	8
7.9 Information to be provided by the manufacturer	9
8 Marking of the tub or tray	9
9 Labelling	10
Annex A (informative) Design of tub	11
Annex B (informative) Design of nest	12
Annex C (informative) Design of tray	13
Annex D (normative) Glide force test method to evaluate cartridge lubrication	14
Annex E (informative) Schematic illustrations of examples for the orientation of tubs or trays within the protective bag	16
Annex F (normative) Closure systems liquid leakage	19
Annex G (informative) Sample preparation for endotoxin and particulate determination	21
Annex H (informative) Product and packaging configuration	25
Bibliography	28

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).

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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 13926-1 specifies the design, dimensions, materials, performance and test methods for glass cylinders used with pen-injectors for medical use.

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 have started to develop such systems of this type for cartridges.

The availability of two packaging configurations makes ready for filling glass cartridges suitable for use 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.

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Sterile packaged ready for filling glass cartridges

1 Scope

This document specifies the characteristics of sterile and ready for filling empty glass cartridges 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 8871-1, *Elastomeric parts for parenterals and for devices for pharmaceutical use — Part 1: Extractables in aqueous autoclavates*

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*

ISO 11608-3:2012, *Needle-based injection systems for medical use — Requirements and test methods — Part 3: Finished containers*

ISO 13926-1:2018, *Pen systems — Part 1: Glass cylinders for pen-injectors for medical use*

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

cap

component which attaches the *disc* (3.3) to the cartridge

[SOURCE: ISO 11608-3:2012, 3.1]

3.2

customer

business entity which purchases sterile ready for filling cartridges and conducts further processing or filling as appropriate

3.3

disc

component which seals the end of the container opposite the *plunger* (3.9)

[SOURCE: ISO 11608-3:2012, 3.5]

3.4

filling volume

90 % of the brimful capacity

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

3.5

insert liner

foil to cover and protect the cartridges

3.6

manufacturer

business entity which performs or is otherwise responsible for the manufacturing of the cartridges ready to be filled by the *customer* (3.2)

3.7

nest

plastic plate with a defined hole pattern for the placing of the cartridges

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

3.8

packaging system

combination of the *sterile barrier system* (3.13) and *protective packaging* (3.10)

[SOURCE: ISO 11139:2018, 3.192]

3.9

plunger

elastomeric component which seals the back end of cartridge

3.10

protective packaging

configuration of materials designed to prevent damage to the *sterile barrier system* (3.13) and its contents from the time of their assembly until the point of use

[SOURCE: ISO 11139:2018, 3.219]

3.11

protective bag

plastic bag or sealing around the *tub* (3.15) or the *tray* (3.14)

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

3.12

sealing lid

microbial barrier material for sealing the *tub* (3.15) or the *tray* (3.14)

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

3.13

sterile barrier system

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

3.14**tray**

plastic container with optional supports to accommodate individual cartridges

3.15**tub**

plastic container to accommodate the filled *nest* ([3.7](#))

[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 cartridges 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 cartridges 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 Lubrication

The inner surface of the cartridges can be lubricated. Limit values of the amount of lubricant and the required glide forces are subject to agreement between the manufacturer and the customer. Lubrication of the inner surface of the cartridges is applied in order to improve gliding properties. This is usually done by siliconization, with silicone emulsion followed by heat treatment.

[Annex D](#) specifies a suitable test method for the determination of the quality and consistency of the lubrication using a glide force test.

5.4 Capping and crimping

5.4.1 Cartridges can optionally, upon customer request, be pre-capped with selected rubber formulations. The rubber material that can be in contact with the injectable product shall meet applicable requirements of ISO 8871-1. For additional regional or national requirements of pharmacopoeias, see type I or type II requirements of Ph. Eur. 3.2.9, USP <381>.

5.4.2 The closure system shall provide an appropriate liquid leakage resistance when tested in accordance with [Annex E](#).

5.5 Plunger insertion

If required by the customer, as option of capping and crimping, plunger insertion can be performed by the manufacturer. The rubber constituent shall meet applicable requirements of ISO 8871-1. For additional regional or national requirements of pharmacopoeias, see type I or type II requirements of Ph. Eur. 3.2.9, USP <381> and JP 7.03 that is applicable to volumes > 100 ml.

5.6 Packaging

5.6.1 Non-sterile glass cartridges already washed, shall be packed in plastic trays or nest and tub configuration as agreed between the manufacturer and the customer. See [Annex H](#).

5.6.2 For packaging systems for sterilized ready for filling cartridges, see [Clause 7](#).

5.7 Sterilization

5.7.1 Sterilized ready for filling cartridges 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).

5.7.2 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 [\[20\]](#).

6 Requirements for glassware

6.1 General

Cartridges 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 13926-1. 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 cartridges made of glass tubing should meet the requirements of ISO 13926-1:2018, Figure 1 and Table 1. Dimension of cartridges for different applications not included in ISO 13926-1 can be acceptable if agreed upon with the customer.

6.4 Particles

6.4.1 Visible particles

Sterilized cartridges 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 materials. 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 G](#).

NOTE 1 See also Ph. Eur. 2.9.19, Ph. Eur. 2.9.20, USP <788>, JP 6.06 as well as 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 $\geq 10\ \mu\text{m}$: 600 max. per container;
 - particles $\geq 25\ \mu\text{m}$: 60 max. per container.
- b) if determined by using the microscopic particle count test (see USP <788> Method 2):
 - particles $\geq 10\ \mu\text{m}$: 300 max. per container;
 - particles $\geq 25\ \mu\text{m}$: 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 cartridges shall be < 0,25 EU/ml considering the filling volume. For sample preparation for endotoxin determination, see [Annex G](#).

6.5.2 The cartridges 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 according to 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 cartridges shall protect the cartridges 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 cartridges into an aseptic filling environment and related designated cleanrooms.

NOTE The introduction of sterilized packaged cartridges 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 cartridges 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) plunger insertion;
 - 4) capping and crimping;
 - 5) stacking and destacking.
- c) for protective bags:
 - 1) sealing;
 - 2) folding;
 - 3) decontamination;
 - 4) cutting and opening.

7.1.6 The packaging configuration including the arrangement of the product shall be agreed with the customer to allow for adequate usability through the required processes.

NOTE The process steps described include those at the premises of the manufacturer and of the customer.

7.2 Nest and tub configuration

7.2.1 Ready for filling glass cartridges shall be packaged in a rigid plastic nest, which is placed within a rigid plastic tub.

7.2.2 The nest shall maintain distance between the glass cartridges to reduce breakage during transportation. Cartridge orientation shall be agreed upon between the manufacturer and the customer. Depending on a particular cartridge's dimensions, nests can contain different numbers and sizes of wells. The tub shall maintain the nest in the correct position.

7.2.3 The cartridges shall be covered with a protective insert liner and the tub shall be sealed with a sealing lid. The assembly shall be thermo-welded by heating the sealing lid. Once sealed, the tub and lid assembly shall serve as a sterile barrier system to maintain sterility of the contents following sterilization of the packaging system.

7.3 Tray configuration

7.3.1 Ready for filling cartridges shall be packaged directly into the tray that can be considered the plastic support.

7.3.2 The tray can be equipped with some plastic insertions to guarantee the right orientation of the cartridges and physical separation between the glass cartridges to reduce breakage during transportation. The cartridge orientation shall be agreed upon between the manufacturer and the customer.

NOTE Depending on a particular cartridge dimension, trays can contain varying numbers of cartridges.

7.3.3 The cartridges shall be covered with a protective insert liner and the tray shall be sealed with a thermo-welded sealing lid. Once sealed, the tray and sealing lid serve as a sterile barrier system to maintain sterility of the containers, following sterilization of the packaging system.

7.4 Nest

7.4.1 For the nest, the following information should be provided (information on dimensions including tolerances):

- external dimensions;
- cavities for the cartridges;
- centring/lifting features (i.e. openings, columns);
- defined free space where the lifting tool can engage.

7.4.2 Customer and manufacturer shall agree upon the dimensions and tolerances of the finished product as delivered. For information, see [Annex B](#).

7.5 Tub and tray

7.5.1 For tubs and trays, the following information should be provided to the customer (information on dimensions including tolerances):

- external dimensions including reinforcements, radii and indentations;
- dimensions of the reinforcement below the sealing edge as well as the slope of the lateral surfaces.

7.5.2 The tub and tray shall allow the sealing of the sealing lid.

7.5.3 The tub and tray flange shall be free of sharp edges to protect the integrity of the various packaging layers.

7.5.4 If sterilization indicators are applied to the tubs or tray, they shall comply with ISO 11138 (all parts) and ISO 11140 (all parts).

Customer and manufacturer shall agree upon the dimensions and tolerances of the finished product as delivered.

NOTE For information, see [Annex A](#) and [Annex C](#).

7.6 Insert liner

7.6.1 Insert liner shall be used to protect the cartridges from particles generated during opening the tub or tray. The insert liner shall be, where appropriate, permeable for the sterilization agent (e.g. made of nonwoven material of polyolefin).

7.6.2 The insert liner can consist of several layers. To enable proper removal, the layers should be connected with each other (e.g. by means of sealing points).

7.6.3 Edges can be rounded. The shape and dimensions of the insert liner shall match with the tub or the tray shape and dimensions.

7.7 Sealing lid

7.7.1 The sealing lid (e.g. made from nonwoven polyolefin material) shall be sealable to the tub or tray and completely peelable from the tub while minimizing the risk of releasing particles. The seal properties (e.g. seal strength, seal width) and integrity shall be tested in accordance with a validated test method. For examples of test methods, see ISO 11607-1.

7.7.2 The sealing lid should be designed to ensure sealing lid overhang beyond the edge of the sealing in order to reduce the risk of delamination.

7.7.3 The sealing lid shall be, where appropriate, permeable for the sterilization agent.

7.7.4 Attention shall be paid to the compatibility of materials and seals with the decontamination processes (e.g. electron beam and vaporized hydrogen peroxide) prior to transfer of the packaging into the aseptic filling area.

7.8 Protective bag

7.8.1 The protective bag shall be permanently sealed and shall enable the selected sterilization method. Testing of the seal properties (e.g. seal strength, seal width) shall be performed in accordance

with a validated test method. For examples of test methods, see ISO 11607-1. As a minimum, the protective bag protects the tub or tray from external contaminants like dust or dirt. It can also be configured as a sterile barrier system to maintain tub or tray sterility over its shelf-life or to allow for bioburden control at time of use.

7.8.2 Attention shall be paid to the selection of materials and seals with regard to decontamination processes (e.g. electron beam and vaporized hydrogen peroxide disinfection) prior to transfer of the packaging into the aseptic filling area.

7.8.3 The protective bag can consist of a single bag or of a double bag. The following information shall be provided as a minimum to the customer (information on dimensions including tolerances).

For single bags:

- bag dimensions (inside and outside);
- width of the sealing joints, in millimetres, their positions, and type of sealing;
- material (type and position, i.e. which material is used at which position);
- orientation of the tub or tray inside the bag, for possible configurations (see [Annex E](#)).

For double bags:

- dimensions of the outer bag;
- width of the sealing joints, in millimetres, their positions, and type of sealing;
- material (type and position, i.e. which material is used at which position) of the outer bag;
- folding of the inner bag.

7.9 Information to be provided by the manufacturer

The manufacturer shall provide the following additional information:

- information about the location of window(s) in the protective bag, if relevant;
- information about specific material characteristics.

8 Marking of the tub or tray

The tub or tray shall be marked as agreed upon between the manufacturer of the sterilized ready for filling cartridges and the customer and can contain the following information:

- a) manufacturer's name;
- b) article description;
- c) quantity of sterilized cartridges ready for filling;
- d) warning "do not use if packaging is damaged";
- e) date of manufacture;
- f) manufacturer's batch number;
- g) serial number.

NOTE 1 Machine-readable codes support automated processing and tracking.

NOTE 2 Symbols according to ISO 7000 or ISO 15223-1 can be used.

9 Labelling

The external packaging shall be marked as agreed upon between the manufacturer of the sterilized cartridges ready for filling and the customer and can contain the following information:

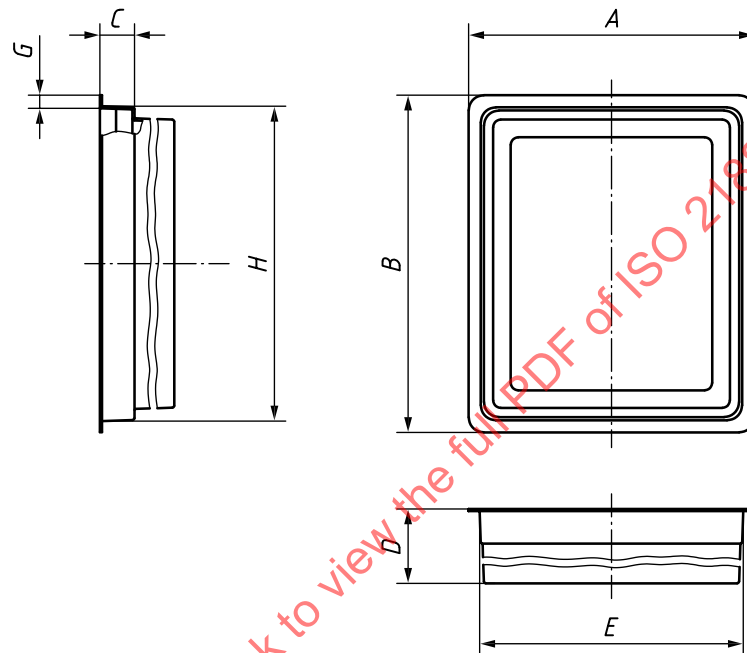
- a) manufacturer's name;
- b) article description;
- c) quantity of sterilized cartridges ready for filling;
- d) date of manufacture;
- e) manufacturer's batch number.

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Annex A (informative)

Design of tub

Figure A.1 shows a schematic design and the nominal dimensions of tubs.



Key

<i>A</i>	220 mm to 227 mm
<i>B</i>	259 mm to 261 mm
<i>C</i>	26 mm to 57 mm
<i>D</i>	88 mm to 98 mm
<i>E</i>	200 mm to 204 mm
<i>G</i>	8 mm to 13 mm
<i>H</i>	232 mm to 244 mm

NOTE 1 These dimensions represent a range of nominal values that reflect the current market situation. Nominal dimensions and tolerances are subject to agreement between the manufacturer and the customer.

NOTE 2 Dimensions refer to material before sterilization or other treatment as for example washing or decontamination.

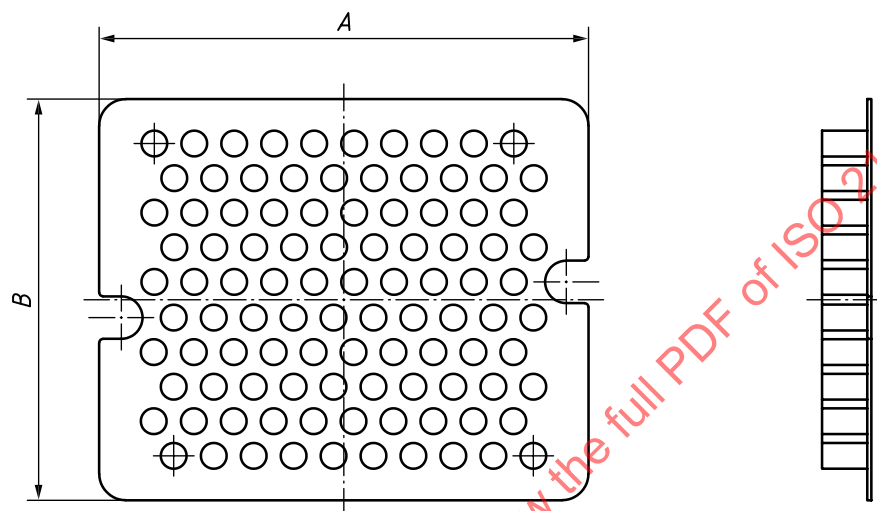
NOTE 3 In comparison to ISO 11040-7, the dimension *F* is not defined in this document.

Figure A.1 — Design of tub for cartridges

Annex B (informative)

Design of nest

Figure B.1 shows a schematic design of a nest, not reflecting the actual cavities and features to hold the cartridges in the cavities and the dimensions for the format A and format B.



Key

- A 229 mm to 238 mm
- B 189 mm to 199 mm

NOTE 1 Concerning the cavities, the geometry and design differ from manufacturer to manufacturer.

NOTE 2 These dimensions represent a range of nominal values that reflect the current market situation. Nominal dimensions and tolerances are subject to agreement between the manufacturer and the customer.

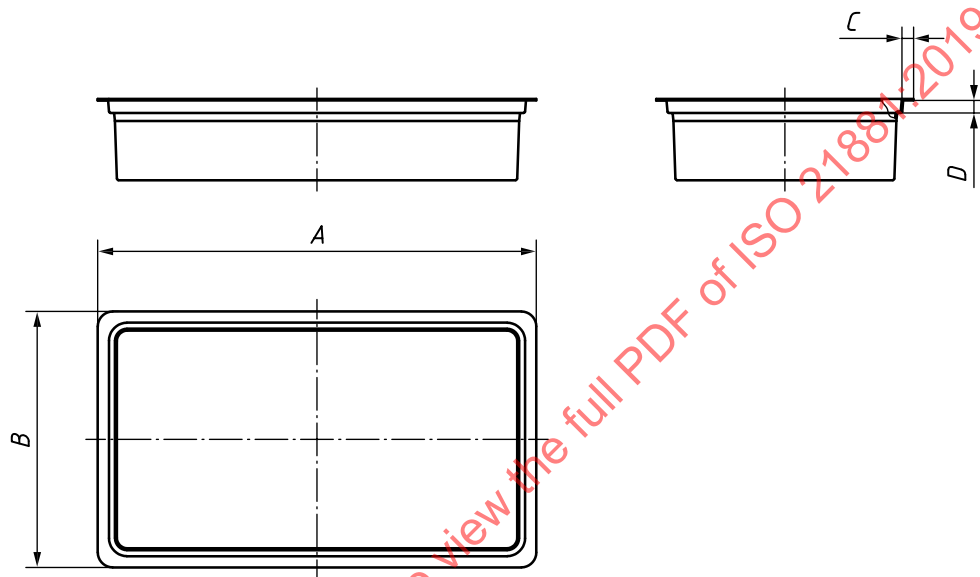
NOTE 3 Dimensions refer to material before sterilization or other treatment as for example washing or decontamination.

Figure B.1 — Design of nest for cartridges

Annex C (informative)

Design of tray

Figure C.1 shows a schematic design of a tray, not reflecting the actual design and cavities and the nominal dimension of tray.



Key

- A 377 mm to 381 mm
- B 219 mm to 225 mm
- C 8 mm to 13 mm
- D 8 mm to 13 mm

NOTE 1 These dimensions represent a range of nominal values that reflect the current market situation. Nominal dimensions and tolerances are subject to agreement between the manufacturer and the customer.

NOTE 2 Dimensions refer to material before sterilization or other treatment as for example washing or decontamination.

Figure C.1 — Design of tray

Annex D (normative)

Glide force test method to evaluate cartridge lubrication

D.1 Purpose

This test method is used to measure the glide force of empty glass cartridges.

The test has been selected based on the test of plunger force and glide force on ISO 11040-4:2015, Annex E.

D.2 Materials

D.2.1 Empty sterilized cartridge ready for filling, numbers as required.

D.2.2 Plunger stoppers (piston) to be agreed upon between the manufacturer and the customer (dimensions, compound, lubrication level, sterilization method).

D.3 Apparatus

D.3.1 Universal tensile and compression test machine conforming with the following:

- Test speed of 100 mm/min or as appropriate;
- Force range up to 50 N or as appropriate.

NOTE Definition of test speed and force range is subject to agreement between the manufacturer and the customer.

D.3.2 Support and cartridge adaptor plates, appropriately sized for the sterilized cartridges ready for filling to be tested (see [Figure D.1](#)).

D.4 Procedure

D.4.1 Set the plunger stopper in the empty cartridges.

D.4.2 If preassembled, remove the cap and the disc.

D.4.3 Place the lubricated cartridges in the adaptor plate on the force-measurement instrument.

D.4.4 Put in contact the loading pin or plunger rod with the plunger stopper.

D.4.5 Start the movement at the designated speed.

D.4.6 End the test when the plunger stopper comes into contact with the shoulder of the cartridges.

D.4.7 Repeat the steps [D.4.1](#) to [D.4.6](#) for additional test samples.

D.4.8 Record the maximum force in the glide force test region. The glide force test region is defined as the region between the break loose until the sharp increase of the force at the end of the stroke. For more information, see ISO 11040-4:2015, Annex E.

Limit values should be agreed between the manufacturer and the customer.

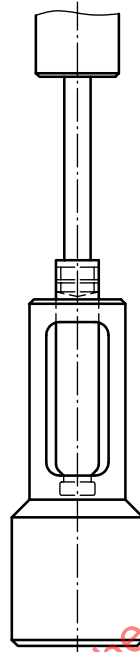


Figure D.1 — Example of the cartridge holder

Annex E (informative)

Schematic illustrations of examples for the orientation of tubs or trays within the protective bag

The schematic illustrations shown in [Figures E.1 to E.6](#) represent examples for the orientation of tubs or trays within the protective bags. The long dimension of the tub or tray should be aligned with the long dimension of the protective bag.

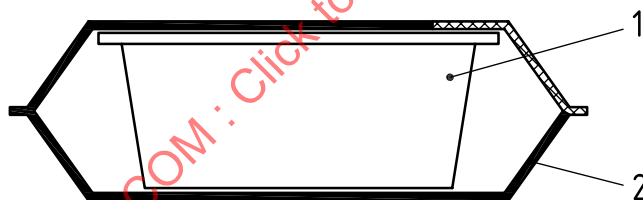
For the dimensions of tubs and trays, see [Annex A](#) and [Annex C](#).



Key

- 1 tub or tray
- 2 protective bag

Figure E.1 — Example 1 — Top web porous material



Key

- 1 tub or tray
- 2 protective bag

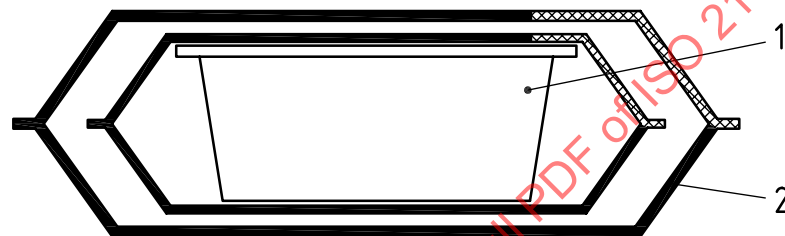
Figure E.2 — Example 2 — Header bag upwards

**Key**

- 1 tub or tray
- 2 protective bag

NOTE This configuration reduces the permeability for sterilization gases versus the configuration in [Figures E.1](#) and [E.2](#) and can have an impact on sterilization cycles.

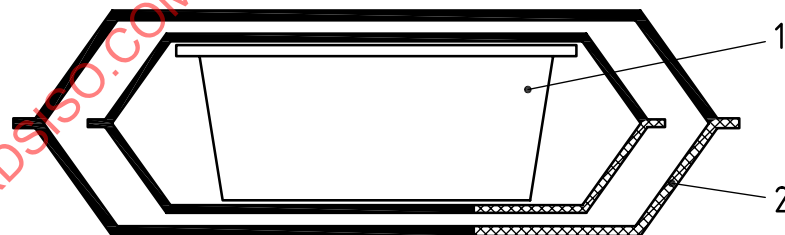
Figure E.3 — Example 3 — Header bag downwards

**Key**

- 1 tub or tray
- 2 protective bag

NOTE Header bag or reel bag windows are located on top of each other to allow for sufficient permeability for sterilization gases and air.

Figure E.4 — Example 4 — Double bag upwards

**Key**

- 1 tub or tray
- 2 protective bag

NOTE Header bag or reel bag windows are located on top of each other to allow for sufficient permeability for sterilization gases and air.

Figure E.5 — Example 5 — Double bag downwards



Key

- 1 tub or tray
- 2 protective bag

Figure E.6 — Example 6 — Double reel bag

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Annex F (normative)

Closure systems liquid leakage

F.1 Principle

The test is used to assess the liquid leakage resistance of cartridges that are pre-crimped with closure systems (cap and disc).

It is mainly designed to verify whether the closure system is able to withstand any potential overpressure inside the cartridge during the filling process.

The test pressure has been selected based on the test of leakage test on ISO 13926-3 and on the test closure system liquid leakage test in ISO 11040-4:2015.

F.2 Materials

F.2.1 Empty ready for filling cartridges, numbers as required.

F.2.2 Plunger stoppers (piston) in ready for filling condition (washed, lubricated and sterilized), to be agreed upon between the manufacturer and the customer (dimensions, compound, lubrication level, sterilization method).

F.3 Apparatus

F.3.1 Universal tensile and compression testing machine conforming with the following:

- test speed of 100 mm/min or as appropriate;
- force range up to 50 N or as appropriate.

NOTE Definition of test speed and force range is subject to agreement between the manufacturer and the customer.

F.3.2 Support and cartridge adaptor plates, appropriately sized for cartridges to be tested.

F.4 Procedure

F.4.1 Fill the test sample to between 1/3 and 2/3 of the nominal fill volume with distilled water or water of equivalent purity.

NOTE The water can be coloured in order to improve the visibility of the leakage.

Apply an axial force for 1 min using [Formula \(F.1\)](#) to calculate the force to be used:

$$F = 0,64 \times d^2 \quad (F.1)$$

where

F is the force, in N;

0,64 is a coefficient expressed in N/mm²;

d is the inner diameter cartridge, according to ISO 11608-3:2012, Figure 2, d_2 , in mm.

F.4.2 Monitor the test samples for leakage during and after the test.

F.5 Expression of results

The test is passed if the caps are not falling off and if no droplets are visible around the surfaces of the cap and disc (seals) closure system.

Visually examine if the test samples have passed or failed the test.

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Annex G (informative)

Sample preparation for endotoxin and particulate determination

G.1 Endotoxins

G.1.1 General

The sample preparation for endotoxin determination is based on the following documents:

- AAMI ST72:2011;
- USP <161>;
- USP <85>;
- USP <660>.

G.1.2 Materials and equipment

G.1.2.1 Sterilized cartridges (i.e. sterilized by ethylene oxide or moist heat), not less than 3 and not more than 10 cartridges.

G.1.2.2 Plunger precapped to cartridge or separate, endotoxin-free or has a defined maximum endotoxin level (e.g. by product certificate).

G.1.2.3 Disc precapped to cartridge or separate, endotoxin-free or has a defined maximum endotoxin level (e.g. by product certificate).

G.1.2.4 Endotoxin-free water of injection or *Limulus Amebocyte Lysate (LAL)* reagents, as extraction fluid having a temperature of $(37 \pm 1) ^\circ\text{C}$ or at least room temperature.

G.1.2.5 Shaker.

G.1.2.6 Endotoxin-free container.

G.1.3 Procedure

G.1.3.1 Protect the endotoxin-free container from environmental contamination until analysed, i.e. work in a controlled environment, e.g. ISO 5 according to ISO 14644-1.

G.1.3.2 If cartridges are neither pre-capped or pre-plungered stoppered, close cartridge on one side by capping or plungering.

G.1.3.3 Fill the cartridges with extraction fluid up to the filling volume that is the 90 % of the brimful capacity of the cartridge.

G.1.3.4 If pre-capped (5.4), close the cartridges with the plunger; if pre-plungered (5.5) close the cartridges by capping.

Air bubble entrapment is recommended to be avoided while capping or plunging, but not critical for endotoxin result.

G.1.3.5 Store the filled and closed cartridges for not less than 1 h at room temperature.

G.1.3.6 Shake the cartridges vigorously for 10 min on a horizontal shaker (or similar device).

G.1.3.7 Dispense the contents of the cartridges into endotoxin-free container by means most appropriate for cartridge opening/dispensing at minimized risk for cross contamination.

G.1.3.8 Determine the number of endotoxin units (EU/ml) of the extract using the method as given in USP <85> including “positive” and “negative” samples.

The limit of the extraction fluid can be calculated using [Formula \(G.1\)](#):

$$\frac{K \times N}{V} \quad (G.1)$$

where

K is the amount of endotoxin allowed per cartridge;

N is the number of devices tested;

V is the total volume of extract rinse.

Ensure that the sensitivity of test reagent is high enough to allow a proper detection limit of endotoxins for pooled samples.

EXAMPLE For 1 ml filling volume and an endotoxin limit < 0,25 EU/ml and a sensitivity of the reagent of 0,02 EU/ml, the “alarm” limit for 10 pooled cartridges would be 0,20 EU/ml which is < 0,25 EU/ml.

G.2 Particulates

G.2.1 General

The sample preparation for endotoxin determination of particulates is based on USP <788> [D] and Ph.Eur.2.9.19 [E].

G.2.2 Materials and equipment

G.2.2.1 Sterilized cartridges (i.e. sterilized by ethylene oxide or moist heat), number as required.

G.2.2.2 Plunger precapped to cartridge or separate, particle-free or has a defined maximum endotoxin level (e.g. by product certificate).

G.2.2.3 Disc precapped to cartridge or separate, particle-free or has a defined maximum endotoxin level (e.g. by product certificate).

G.2.2.4 Water, for injection or any grade of purified water.

G.2.2.5 Container.