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Prefilled syringes —

Part 7: Packaging systems for sterilized subassembled syringes ready for filling

Seringues préremplies —

Partie 7: Systèmes d'emballage pour les seringues stérilisées prêtes à l'emploi préremplissables

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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.

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 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*.

ISO 11040 consists of the following parts, under the general title *Prefilled syringes*:

— *Part 1: Glass cylinders for dental local anaesthetic cartridges*

— *Part 2: Plunger stoppers for dental local anaesthetic cartridges*

— *Part 3: Seals for dental local anaesthetic cartridges*

— *Part 4: Glass barrels for injectables and sterilized subassembled syringes ready for filling*

— *Part 5: Plunger stoppers for injectables*

— *Part 6: Plastics barrels for injectables*

— *Part 7: Packaging systems for sterilized subassembled syringes ready for filling*

The following part is under preparation:

— *Part 8: Requirements and test methods for finished prefilled syringes*

Introduction

At the start of prefilled syringe processing by the pharmaceutical industry, syringes made of tubing glass were delivered to the pharmaceutical companies in the form of a so called non-sterile “bulkware” only. The process steps like washing, drying, inner lubrication, sealing the syringe with a closure system, sterilization, as well as filling, and closing were then performed in the pharmaceutical companies. Processing of “bulkware” is still performed like this nowadays. Sterilized subassembled syringes have partially replaced the non-sterile “bulkware”.

In the case of sterilized subassembled syringes ready for filling, responsibility for the aforementioned process steps relevant to the injectable product lies within the manufacturer of the primary packaging material. Following the assembly of the needle shield on syringes with a staked needle or tip caps for the luer cone version, the subassembled syringes are placed into so called nests. The nests, in turn, are placed into a plastic tub. The syringes in the nest are protected by means of an insert liner and the tub itself is sealed by a sealing lid (which is currently, and so far, primarily achieved using a porous material). Thus, the tub properly sealed with the sealing lid represents the “sterile barrier system”. The sealed tub is then wrapped into a sealable bag and, thus, ready for sterilization which is currently, and so far, primarily performed using ethylene oxide.

In this form, the sterilized subassembled syringes ready for filling are delivered to the pharmaceutical companies in a sterile condition where they are processed on suitable machines.

The packaging design and material have to ensure sterility and should be compatible with the process of the customer. The packaging characteristics, material, thickness, shape, and resistance to deformations among others are such that they maintain, up to the point of use, the integrity of the product and a validated barrier against particulate and bacterial contamination. The packaging materials have to fulfil regional and national regulatory requirements.

Prefilled syringes —

Part 7: Packaging systems for sterilized subassembled syringes ready for filling

1 Scope

This part of ISO 11040 specifies the packaging system that is used to deliver sterilized subassembled syringes ready for filling in tubs and nests.

Downstream processes (processes after filling such as in house/outside transport, reprocessing) can result in specific requirements on the packaging system used to deliver sterilized subassembled syringes ready for filling. However, these requirements are not within the scope of this part of ISO 11040.

NOTE 1 Glass barrels and sterilized subassembled syringes ready for filling, plungers, and plastic barrels for injectables are specified in ISO 11040-4, ISO 11040-5, and ISO 11040-6.

NOTE 2 ISO 11607-2 addresses validation requirements of sealing and packaging processes for medical devices.

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 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.

3.1
customer
business entity which purchases syringe barrels or sterilized subassembled syringes ready for filling and conducts further processing or filling as appropriate

3.2
insert liner
foil to cover the filled nest

3.3
manufacturer
business entity which performs or is otherwise responsible for the manufacturing of the syringe barrels (bulkware) or for the sterilized subassembled syringes ready for filling by the customer

3.4
nest
plastic plate with a defined hole pattern for the suspension of the syringe bodies

3.5
primary packaging material
packaging materials used in pharmaceutical packaging which will contain, seal, or be used for dose application of a medicinal product and which will have direct contact with the medicinal product

[SOURCE: ISO 15378:2011, definition 3.35.1]

3.6
protective bag
plastic bag or sealing around the tub

3.7
sealing lid
microbial barrier material for sealing the tub

3.8
packaging system
combination of the sterile barrier system and protective packaging

[SOURCE: ISO/TS 11139:2006, definition 2.28]

3.9
protective packaging
configuration of materials designed to prevent damage to the sterile barrier system and its contents from the time of their assembly until the point of use

[SOURCE: ISO/TS 11139:2006, definition 2.37 modified by adding "from the time of their assembly".]

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

Note 1 to entry: For packaging systems for sterilized subassembled syringes ready for filling, the sterile barrier system is formed by the tub and sealing lid.

[SOURCE: ISO/TS 11139:2006, definition 2.44 modified by adding Note 1 to entry.]

3.11
tub
plastic container to accommodate the filled nest

4 Requirements for the packaging system

4.1 General

4.1.1 The introduction of sterilized packaged subassembled syringes into an aseptic filling environment poses a risk of microbiological and/or particulate contamination of the drug product. The packaging system shall have acceptable microbiological and particulate levels to support the introduction of the sterilized subassembled syringes into an aseptic filling environment. Requirements should be agreed upon by the manufacturer and the customer.

4.1.2 The materials, the sterile barrier system, and the packaging system that enable sterilization and maintain sterility until the point of aseptic filling shall comply with the requirements of ISO 11607-1. The sterile barrier system shall ensure product sterility over its shelf-life (i.e. the time sterility is ensured by the integrity of the sterile barrier system in recommended storage conditions). As a minimum, the protective bag protects the tub from external contaminants like dust or dirt. Ideally, it also maintains product sterility over its shelf-life and allows for bioburden control at the time of use.

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

a) for tubs including sealing lid and insert liner:

   1) lid sealing and lid opening;

   2) conveying;

   3) nest insertion and extraction;

   4) stacking and destacking;

   5) sterilization (e.g. ethylene oxide, gamma) and decontamination (e g. electron beam).

b) for nests:

   1) barrel insertion and extraction;

   2) filling;

   3) stoppering;

   4) stacking and destacking.

c) for protective bag:

   1) sealing;

   2) folding;

   3) decontamination;

   4) cutting and opening.

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

4.2 Nest

NOTE This subclause covers nests used for sterilized subassembled syringes ready for filling. Nested formats can also be used for plunger stoppers/pistons.

4.2.1 For the nest, the following information shall be provided (information on dimensions including tolerances):

— external dimensions;

— deflection;

— holes for the syringes;

— centering openings/lifting openings;

— defined free space where the lifting tool can engage.

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

NOTE For information on dimensions, see Annex A. This annex has the intent to harmonize products coming to the market to facilitate the handling and processing of the prefilled syringes.

4.2.2 The design of the nest shall facilitate the insertion and removal of the sterilized subassembled syringes ready for filling (e.g. Luer lock adapter (LLA)-syringes) by adding bevels or other means.

NOTE For information on design, see Annex A.

4.2.3 The maximum acceptable nest deflection should be agreed upon by the manufacturer and customer. The nest deflection can be determined using the test method as described in Annex B.

4.3 Tub

4.3.1 For tubs, the following information shall be provided (information on dimensions including tolerances):

— external dimensions including reinforcements/beads, radii, and indentations;

— dimensions of the reinforcement/bead below the sealing edge, as well the slope of the lateral surfaces.

NOTE For information on dimensions, see Annex C. This annex has the intent to harmonize products coming to the market to facilitate the handling and processing of the prefilled syringes.

4.3.2 The tub shall allow the sealing of the lid.

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

NOTE For information on design, see Annex C.

4.3.3 If sterilization indicators are applied to the tubs, they shall comply with the appropriate International Standards (see ISO 11138 and ISO 11140).

4.4 Insert liner

The insert liner that is intended to protect the syringes from particles generated during opening should release a minimum of particles. The insert liner shall be, where appropriate, permeable for the sterilization agent (e.g. made of non-woven material of polyolefine).

The insert liner can consist of several layers in order to ensure sufficient shielding of the glass against electron beam irradiation during the decontamination process. To enable proper removal, the layers should be connected with each other (e.g. by means of sealing the points).

Edges may be rounded. The shape and dimensions of the insert liner shall comply with the tub.

4.5 Sealing lid

The sealing lid (e.g. made from non-woven polyolefin material) shall be sealable to the tub 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.

NOTE For examples of test methods, see ISO 11607-1.

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.

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

Considerations should be given to the selection of materials and seals with regard to decontamination processes (e.g. electron beam disinfection) prior to transfer of the packaging into the aseptic filling area.

4.6 Protective bag

4.6.1 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.

NOTE For examples of test methods, see ISO 11607-1.

Considerations should be made to the selection of materials and seals with regard to decontamination processes (e.g. electron beam and H_2O_2 disinfection) prior to transfer of the packaging into the aseptic filling area.

4.6.2 The protective bag can consist of a single bag or double bags. 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, and their positions and type of sealing;

— material (type and position, i.e. which material is used at which position);

— orientation of the tub inside the bag (for possible configurations, see Annex D).

For double bags:

— dimensions of the outer bag;

— width of the sealing joints, in millimetres, and their positions and type of sealing;

— material (type and position, i.e. which material is used at which position) of the outer bag;

— orientation of the tub with the bag inside the outer bag (for possible configurations, see Annex D);

— folding of the inner bag.

NOTE For types of protective bags, including dimensions, see Annex E.

5 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.

6 Marking of the tub

The tub shall be marked as agreed upon by the manufacturer of the sterilized subassembled syringe ready for filling and the customer and can contain the following information:

a) manufacturer's name;

b) article description;

c) quantity of sterilized subassembled syringes ready for filling;

d) warning "do not use if packaging is damaged";

e) date of manufacture;