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Needle-based injection systems for medical use — Requirements and test methods —

Part 3: Containers and integrated fluid paths

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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 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 84, *Devices for administration of medicinal products and catheters*, in collaboration with the European Committee for Standardization (CEN) Technical Committee CEN/TC 205, *Non-active medical devices*, in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

This third edition cancels and replaces the second edition (ISO 11608-3:2012), which has been technically revised.

The main changes are as follows:

— Test methods and dimensions specific to traditional pen-injector “Type A” cartridges have been removed.

A list of all parts in the ISO 11608 series can be found on the ISO website.

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

Developers and manufacturers of NIS are encouraged to investigate and determine if there are any other requirements relevant to the safety of their products.

Previous editions of this document focused on multi-dose pen-injector cartridges, important dimensions (e.g. inner diameter) and related attributes (e.g., disc seal eccentricity, meniscus) deemed critical for pen-injector form, fit, and function. The previous edition (i.e. ISO 11608-3:2012) included a more general discussion of "other containers" like syringes given their role in single dose NIS with automated functions (commonly referred to as auto-injectors).

Needle-based injection systems for medical use — Requirements and test methods —

Part 3:
Containers and integrated fluid paths

1 Scope

This document specifies requirements and test methods for design verification of containers and integrated fluid paths used with Needle-Based Injection Systems (NISs) according to ISO 11608-1.

It is applicable to single and multi-dose containers either filled by the manufacturer (primary container closure) or by the end-user (reservoir) (e.g. cartridges, syringes) and fluid paths that are integrated with the NIS at the point of manufacture.

This document is also applicable to prefilled syringes (see ISO 11040-8) when used with a NIS (see also scope of ISO 11608-1:2021).

This document is not applicable to the following products:

— sterile hypodermic needles;

— sterile hypodermic syringes;

— sterile single-use syringes, with or without needle, for insulin;

— containers that can be refilled multiple times;

— containers intended for dental use;

— catheters or infusion sets that are attached or assembled separately by the user.

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 7864:2016, *Sterile hypodermic needles for single use — Requirements and test methods*

ISO 8872, *Aluminium caps for transfusion, infusion and injection bottles — General requirements and test methods*

ISO 9626:2016, *Stainless steel needle tubing for the manufacture of medical devices — Requirements and test methods*

ISO 10555-1:2013, *Intravascular catheters — Sterile and single-use catheters — Part 1: General requirements*

ISO 10555-5:2013, *Intravascular catheters — Sterile and single-use catheters — Part 5: Over-needle peripheral catheters*

ISO 10993-11, *Biological evaluation of medical devices — Part 11: Tests for systemic toxicity*

ISO 10993-17, *Biological evaluation of medical devices — Part 17: Establishment of allowable limits for leachable substances*

ISO 11040-4, *Prefilled syringes — Part 4: Glass barrels for injectables and sterilized subassembled syringes ready for filling*

ISO 11040-5, *Prefilled syringes — Part 5: Plunger stoppers for injectables*

ISO 11040-6, *Prefilled syringes — Part 6: Plastic barrels for injectables and sterilized subassembled syringes ready for filling*

ISO 11040-8, *Prefilled syringes — Part 8: Requirements and test methods for finished prefilled syringes*

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

ISO 11608-1:2021, *Needle-based injection systems for medical use — Requirements and test methods — Part 1: Needle-based injection systems*

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

ISO 13926-2, *Pen systems — Part 2: Plunger stoppers for pen-injectors for medical use*

ISO 13926-3, *Pen systems — Part 3: Seals for pen-injectors for medical use*

ISO 21881, *Sterile packaged ready for filling glass cartridges*

ISO 80369-7, *Small-bore connectors for liquids and gases in healthcare applications — Part 7: Connectors for intravascular or hypodermic applications*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 11608-1 and the following apply.

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

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

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

3.1
cartridge
container for the medicinal product that is closed on one end with a *cartridge cap* (3.2) and *disc* (3.5), and on the other end with a *plunger stopper* (3.8)

3.2
cartridge cap
component that attaches the *disc* (3.5) to the *cartridge* (3.1)

3.3
container closure integrity
CCI
adequacy of primary container closure to maintain a *sterile barrier* (3.10) against potential contaminants until the labelled expiration date or first intentional user interaction

3.4
fragmentation
formation of elastomeric particles that are generated when the *disc* (3.5) or other elastomeric components that forms part of the primary container closure is pierced by a needle, spike or other access device for filling or delivery

Note 1 to entry: Disc coring is one mechanism to generate fragments.

3.5
disc
septum
elastomeric closure
component of a container [typically a *cartridge* (3.1)], which seals the end of the container through which the medicinal product is accessed

3.6
integrated fluid path
needle-based injection system pathway (NIS), integrated into the NIS at the time of manufacture, that the medicinal product follows from the container or reservoir to the targeted delivery site

3.7
medicinal product compatibility
evaluation of the medicinal product quality based on combined use with the needle-based injection system

Note 1 to entry: Impact of medicinal product on device is covered in ISO 11608-1.

3.8
plunger stopper
component that seals one end of the container and moves within the container to cause or accommodate movement of the medicinal product

3.9
sterility assurance level
SAL
probability of a single viable microorganism occurring after sterilization

Note 1 to entry: It is expressed as the negative exponent to the base 10.

[SOURCE: ISO 11139:2018, 3.275 — modified, "on an item" has been deleted.]

3.10
sterile barrier
system of components that provide a barrier to microbial ingress

4 Requirements

4.1 General

These requirements apply to containers or integrated fluid paths intended to be used with a NIS. When test methods and specifications are noted, they are included to assist manufacturers and suppliers in supporting conformity with design specification of the NIS.

Annex F provides illustrated examples of Primary Container Closures (PCC), reservoirs and fluid path configurations for manufacturer filled and user filled NIS.

Specific requirements for NIS primary container closure system components are:

a) glass syringes (including integrated needles) shall conform with applicable requirements of ISO 11040-4 and ISO 11040-8;

b) plastic syringes (including integrated needles) shall conform with applicable requirements of ISO 11040-6 and ISO 11040-8;

c) prefilled syringes (including integrated needles) shall conform with applicable requirements of ISO 11040-8;

d) syringe plunger stoppers shall conform with applicable requirements of ISO 11040-5;

e) glass cartridges shall conform with applicable requirements of ISO 13926-1 and ISO 21881;

f) cartridge plunger stoppers shall conform with applicable requirements of ISO 13926-2;

g) cartridge discs shall conform with applicable requirements of ISO 13926-3;

h) cartridge caps shall conform with applicable requirements of ISO 8872;

i) all reservoirs provided empty to the user shall be free of droplets of fluid (lubrication) on the outside or inside surfaces when inspected in accordance with ISO 11608-1:2021, 11.3.

4.2 Container integrity

4.2.1 Container Closure Integrity (CCI)

Container closure integrity shall be ensured until the expiration date or the first intentional user interaction that breaks CCI.

If the NIS is manufacturer-assembled with a primary container closure to form a single integral unit, the manufacturing processes, including assembly, shall be shown to not adversely impact container closure integrity, in accordance with applicable pharmacopeia.

4.2.2 Resealability — All multi-dose cartridges or reservoirs with discs

For all cartridges or reservoirs with discs intended for multiple penetrations, after having been penetrated in accordance with the test method specified in 5.1, the penetrated discs of 20 cartridges or reservoirs shall not leak from the penetration site when the cartridge is pressurized.

The disc of the cartridge or reservoir shall be punctured a minimum of 1,0 times the maximum number of penetrations expected during its intended use. Risk assessment shall assess the impact of resealability on the function of the NIS to determine if a greater safety factor is required.

4.2.3 Fragmentation (disc coring) – cartridges or reservoirs with discs

Cartridges or reservoirs that are accessed through an elastomeric disc with a needle, spike or other access device for delivery shall not exceed six elastomeric disc fragments in the visible range (>150 µm in diameter) per 100 punctures in accordance with the method described in 5.2, collected from both coring (ejected from the needle) and fragmentation (collected from the liquid expelled from the container or reservoir).

For single-dose cartridges, a single penetration on each cartridge or reservoir shall be performed.

For multi-dose cartridges or reservoirs, each disc (barrier) shall be punctured a minimum of 1,0 times the maximum number of penetrations expected during its intended use.

Risk assessment shall assess the impact of fragments on the function of the NIS to determine if a greater safety factor, additional mitigations or lowering the limit of allowed fragments shall be required.

NOTE The impact of any fragments on the function of the NIS can be assessed through dose accuracy testing.

4.3 Cannula requirements (as part of the fluid path)

4.3.1 Rigid needles

If the integrated fluid path contains a rigid needle, the strength of union between the needle at its connection point to the NIS shall not break when subjected to the minimum force given in ISO 7864:2016, Table 2 when tested according to ISO 7864:2016, Annex B. The directions of force shall be applied as the needle would encounter during removal from the injection site.

For tapered needles, the minimum force given in ISO 7864:2016, Table 2 shall be determined by the outer diameter at the hub as indicated in ISO 7864:2016, Figure 1.

The performance of the rigid needle part shall fulfil the requirements in ISO 9626:2016, Clause 5 and ISO 7864:2016, 4.10.4 (paragraph 1), 4.11, 4.12 and 4.13, or an equivalent and applicable standard for tubing suited to medical use but fabricated in materials other than stainless steel, to ensure the rigid needle performs as intended for the specific design.

4.3.2 Soft cannulas

If the integrated fluid path contains a soft cannula and an introducer needle, the strength of union between the soft cannula and NIS, or the introducer needle and the NIS, shall meet the requirements of ISO 10555-5:2013, 4.3.3.4 to ensure the soft cannula and/or introducer needle remains affixed to the NIS throughout its intended use. The testing shall consider and address the forces and vectors that the introducer needle and cannula would encounter during removal from the injection site.

In addition, the soft cannula shall meet the requirements of ISO 10555-1:2013, 4.6 to ensure the soft cannula performs as intended for the specific design. Additional physical and functional evaluations to be considered can include flexural fatigue, compression force, kink resistance, burst testing, etc. Risk assessment shall be relied upon to determine appropriate evaluations.

In addition, Annex A can also be of assistance.

4.4 Fluid line connections

If the NIS requires a separate external fluid line to connect the functional core of the NIS to a distant injection site, any connections along that fluid line shall withstand a static tensile force of not less than 15 N for 15 s.

If any connection uses a Luer connection, the connector shall conform with ISO 80369-7.

4.5 Medicinal product compatibility

4.5.1 General

All materials of the NIS in direct contact with the medicinal product shall be compatible with the medicinal product.

When the NIS is filled by the manufacturer, and the container and/or the integrated fluid path are designed to protect the medicinal product through shipment and storage, it shall be considered part of the primary container closure.

NOTE 1 The requirements for assessing the adequacy of the PCC is covered by applicable pharmacopeia and ICH Guidance and are not addressed within this document.

NOTE 2 Annex A provides a reference to some relevant requirements, guidance, standards or compendia material for each topic below.

4.5.2 Medicinal product compatibility with reservoir and integrated fluid path materials

Reservoir and integrated fluid path materials that can come into contact with the medicinal product shall not adversely affect the quality of the medicinal product for the intended time of contact. These requirements apply to the medicinal product after delivery through the NIS.

NOTE Annex E provides a discussion of medicinal product compatibility.

4.5.3 Reservoir and integrated fluid path particulate matter

4.5.3.1 General

The reservoir and/or integrated fluid path shall be assessed for sub-visible and visible particulate matter.

Applicable pharmacopeia establishes limits for the size and number of particulates allowed for the medicinal product. A portion or subset of the particulate matter limit can be generated by the reservoir and/or fluid path during delivery. Manufacturers shall establish particulate matter limits of the reservoir and/or fluid path based on risk assessment and applicable pharmacopeia.

It is recommended that the manufacturer and its supplier agree upon the test methods to be used and the allocation of size and number of sub-visible and visible particulate matter permissible for the NIS.

Particulates, which, due to their size, nature and/or quantity interfere with the function of the NIS, medicinal product compatibility or have a negative impact to patient safety, shall not be acceptable.

NOTE The impact of any particulates on the function of the NIS can be assessed through dose accuracy testing.

4.5.3.2 Sub-visible

Unless otherwise justified, limits for the NIS reservoir and/or integrated fluid path shall be:

— Particles ≥10 µm: 600 max. per NIS;

— Particles ≥25 µm: 60 max. per NIS;

when tested, for example, in accordance with the method described in 5.3.

NOTE These above listed limits are taken from ISO 11040-4:2015.

4.5.3.3 Visible

Visible particulate matter (>150 µm in diameter) other than fragments generated during disc penetration, which are addressed in 4.2.3, for the NIS reservoir and/or integrated fluid path shall not be present when tested, for example, in accordance with the method described in 5.4.

NOTE The above listed limit is taken from United States Pharmacopeia (USP).

4.5.4 Reservoir and fluid path pyrogenicity

4.5.4.1 General

Reservoirs and fluid path NISs shall be nonpyrogenic. Studies for determination of nonpyrogenicity shall be conducted on the final NIS or reservoir and/or integrated fluid path components of the NIS, or both, that have been exposed to all NIS manufacturing processes, including sterilization if applicable.