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

Systèmes d'injection sans aiguille pour usage médical — Exigences et méthodes d'essai

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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 84, *Devices for administration of medicinal products and catheters,* in collaboration with the European Committee for Standardization (CEN) Technical Committee CEN/SS S03, *Syringes,* in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

This second edition cancels and replaces the first edition (ISO 21649:2006), which has been technically revised.

The main changes are as follows:

— changes to update the document to be consistent with the approach and requirements currently in the ISO 11608 series. This includes:

  — use of a risk-based approach to specifications and testing;

  — damp heat testing;

  — water and dust intrusion;

  — transport and lifetime testing.

— changes to address requirements for mass vaccinations such as:

  — requirements to reduce the potential for cross contaminations, such as a requirement for a re-use prevention feature/auto-disable feature for the patient contact portion of a re-usable/ multi-use device;

  — changes to address robustness requirements including long-term repetitive use and for use in harsh environments;

  — inclusion of specific requirement and a test method to address potential transfer of pathogens between patients.

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

This document specifies the results of the design effort instead of the physical and construction requirements used as the basis for device design, so that innovation in achieving the intended purposes is not unnecessarily restricted.

Standards of this nature intentionally avoid addressing more than the most basic elements regarding the safety and performance of NFISs in humans. Any intended labelling of such devices indicating their use to deliver medicinal products into the body or into specified tissue compartments thereof (e.g. intramuscular, subcutaneous or intradermal), or for the administration of specific pharmaceutical drugs or vaccines, falls under the authority of national governments or supranational agencies regulating the manufacture and marketing of medical devices and pharmaceutical products. Despite certain advantages for intentional interchangeability for dose chambers designed for different NFISs, as well as the potential risks of inadvertent interchangeability, these standards avoid setting forth design specifications for the uniform size, shape and interface of such dose chambers.

The sampling plans for inspection selected for this document are intended to verify the design, at a high confidence level, i.e. the manufacturer's ability to manufacture one “lot” of NFISs, which conforms to the critical product attributes. The sampling plan does not replace the more general manufacturing quality systems, including lot release, which appear in standards on quality systems, e.g. ISO 9001or ISO 13485.

This document assumes that each system will be verified and validated for each therapeutic or medicinal product for which it is intended to be used. If the same system is able to, with no or minimal changes, deliver more than one therapeutic or medicinal product, due to the nature and uniqueness of the combination of the delivery system and therapeutic or medicinal product, it will be considered another product and each combination should be addressed individually according to the requirements of this document. This does not preclude leveraging information and data across systems as long as there is sufficient information to support the unique combination under development.

Manufacturers are expected to follow a risk-based approach during the design, development, and manufacture of the NFIS. Given that each product can deliver different medicinal products and/or have a different intended use, this can result in product-specific requirements and test methods that differ from what is outlined in this document. It is expected that a risk management process is applied to justify and document:

— any exclusions/deviations from requirements, specifications, methods or limits contained in or referenced in this document when they are not directly applicable and/or appropriate to the system. These new or modified requirements can be more or less restrictive as they are unique to the specific NFIS (including the medicinal product);

— any substitutions or omissions of requirements, specifications, methods or limits unique to each specific NFIS (including the medicinal product), when those provided in this document are not applicable and/or appropriate to the NFIS.

The flexibility provided in this document allows it to be applied to many different device and medicinal product combinations. However, this makes it difficult to make a general declaration of conformance to the document. As such, when making any declaration of conformance to this document, such deviations, exclusions, substitutions, and omissions should be specified and supported by adequate justification in the design file.

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

1 Scope

This document applies to safety and performance and testing requirements for single-use and multiple-use Needle-Free Injection Systems (NFISs) intended for human use in clinics and other medical settings and for personal use by patients.

The dose chamber of the NFIS is often disposable and intended to be replaced after either a single use or a limited number of uses. It is sometimes separable from the injection mechanism and often termed a "cartridge", "ampoule", "syringe", "capsule" or "disc". In contrast, the dose chamber can also incorporate a permanent internal chamber designed to last through the claimed life of the device, and an additional member or members which eliminate the risk of cross-contamination.

Excluded from this document are drug delivery methods which:

— involve penetration of a part of the device itself into or through skin or mucous membranes (such as needles, tines, micro-needles, implantable slow-release drug devices);

— generate aerosols, droplets, powders or other formulations for inhalation, insufflation, intranasal or oral deposition (such as sprays, inhalers, misters);

— deposit liquids, powders, or other substances on the surface of skin or mucosal surfaces for passive diffusion or ingestion into the body (such as transdermal patches, liquid drops);

— apply sonic or electromagnetic energy (such as ultrasonic or iontophoretic devices);

— infusion systems for adding or metering medication into or through systems of artificial tubes, catheters, and/or needles which themselves enter the body.

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 7886-3:2020, *Sterile hypodermic syringes for single use — Part 3: Auto-disabled syringes for fixed-dose immunization*

ISO 10993 (all parts), *— Biological evaluation of medical devices*

ISO 11201, *Acoustics — Noise emitted by machinery and equipment — Determination of emission sound pressure levels at a work station and at other specified positions in an essentially free field over a reflecting plane with negligible environmental corrections*

ISO 11202, *Acoustics — Noise emitted by machinery and equipment — Determination of emission sound pressure levels at a work station and at other specified positions applying approximate environmental corrections*

ISO 11204, *Acoustics — Noise emitted by machinery and equipment — Determination of emission sound pressure levels at a work station and at other specified positions applying accurate environmental corrections*

ISO 14155, *Clinical investigation of medical devices for human subjects — Good clinical practice*

ISO 14971:2019, *Medical devices — Application of risk management to medical devices*

IEC 60068-2-27, *Environmental testing — Part 2: Tests. Test Ea and guidance: Shock*

IEC 60068-2-31, *Environmental testing — Part 2-31: Tests. Test Ec: Rough handling shocks, primarily for equipment-type specimens*

IEC 60068-2-64, *Environmental testing — Part 2-64: Tests — Test Fh: Vibration, broad-band random and guidance*

IEC 60529, *Degrees of protection provided by enclosures (IP Code)*

IEC 60721-3-7:1995+AMD1:1996, *Classification of environmental conditions — Part 3-7: Classification of groups of environmental parameters and their severities — Portable and non-stationary use*

IEC 61000-4-2:2008, *Electromagnetic compatibility (EMC) — Part 4-2: Testing and measurement techniques — Electrostatic discharge immunity test*

IEC 61000-4-3:2020, *Electromagnetic compatibility (EMC) — Part 4-3: Testing and measurement techniques — Radiated, radio-frequency, electromagnetic field immunity test*

IEC 61672-1, *Electroacoustics — Sound level meters — Part 1: Specifications*

IEC 62366-1, *Medical devices — Part 1: Application of usability engineering to medical devices*

3 Terms and definitions

For the purposes of this document, the following terms and definitions 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
claimed lifetime
total number of injection strokes that a *needle-free injection system* (3.8), in normal use with recommended user maintenance and before manufacturer overhaul or refurbishment of parts, is expected to administer within its *performance profile* (3.11) specified by the manufacturer

Note 1 to entry: This number may also be expressed as a period of time (e.g. number of days, weeks, months or years) at a corresponding frequency of expected usage (e.g. number of injections per day, week, month or year).

3.2
dose chamber
enclosure that contains and is in direct contact with the pharmaceutical product, and from which the pharmaceutical product is administered to the patient by the needle-free injection system

3.3
dose accuracy
difference between the intended dose and the delivered dose

3.4
injection mechanism
components of the *needle-free injection system* (3.8) which are designated to harness, store, regulate, control and transfer to the *dose chamber* (3.2) and/or its contained medicinal product the energies required for the injection to occur, including means to prevent release of such energies, such as a "safety latch"

Note 1 to entry: This term is not used to refer to separate accessories which transfer energy into the needle-free injection system but which are separated from the needle-free injection systems at the time of the injection (such as a separate spring-cocking mechanism, a gas pressurizing tank, a foot pump or other separate device using electricity, muscle power or other energy source).

3.5
intended dose
amount of medicinal product meant to be expelled at one time

3.6
maximum dose
largest amount, which the manufacturer designates the *needle-free injection system* (3.8) is capable of expelling by one injection

3.7
minimum dose
smallest amount, which the manufacturer designates the *needle-free injection system* (3.8) is capable of expelling by one injection

3.8
needle-free injection system
NFIS
injector and its components and accessories that administer a medicinal product to a patient by using mechanical motion (such as movement of a piston or flow of a gas, but not to exclude other means) to impart kinetic energy to the medicinal product, without any part of the system penetrating the skin or mucous membranes

Note 1 to entry: Such components and accessories may include:

— disposable or re-usable *dose chambers* (3.2);

— separable mechanisms that obtain, transfer, convert, or store energy (using hydraulic, pneumatic, mechanical, electrical, chemical or other means);

— filling devices to hold *dose chambers* (3.2) and feed them into the injector or vessels to capture and dispose of used containers;

— instructions and educational materials for end-users.

3.9
nozzle
component of an injector through which the medicinal product is expelled

Note 1 to entry: The nozzle can or cannot, depending on the device design, make physical contact with the skin or other membranes of the patient.

3.10
orifice
hole at the end of the *nozzle* (3.9) through which the medicinal product is expelled

3.11
performance profile
manufacturer-specified set of measurable and quantitative values and tolerance intervals which describes the proper functioning of a *needle-free injection system* (3.8), in order to correctly deliver the medicinal product

3.12
reservoir
intermediate enclosure that holds and has contact with the medicinal product immediately prior to its transfer into the *dose chamber* (3.2)

Note 1 to entry: This container is often the vial or other enclosure filled with the medicinal product by the pharmaceutical manufacturer (and called the "primary packaging" in that industry). It can be single-dose or multi-dose, and usually requires some manipulation by the user, by an accessory filling device, or by the injector device itself to transfer the contents into the *dose chamber* (3.2). There may be no medicinal reservoir for those *needle-free injection systems* (3.8) in which the *dose chamber* (3.2) is pre-filled by the manufacturer of the medicinal product.

3.13
unit container
packaging in which an individual component or *needle-free injection system* (3.8) is provided to a user

4 Symbols

V_{set} Any pre-set dose (expressed as a volume in millilitres) used in determining the dose accuracy for a given NFIS. Specific cases of V_{set} are as follows:

a) minimum dose ($V_{set} = V_{min}$) (specified in the instructions for use);

b) maximum dose ($V_{set} = V_{max}$) (specified in the instructions for use);

c) midpoint dose ($V_{set} = V_{mid}$) where V_{mid} is defined as the NFIS setting closest to:

$(V_{min} + V_{max})/2$.

Recommended doses as specified in the instruction for use may differ from those doses that can be set.

V_{meas} The volumetric measurement value for a given V_{set}, expressed in millilitres

G_{meas} The gravimetric measurement value for a given V_{set}, expressed in grams

ρ Mass density expressed in grams per millilitre

p Probability content

n Number of measurements

$\bar{x}$ The sample mean; when based on a random sample, an estimate of the true mean

s The sample standard deviation; when based on a random sample, an estimate of the true standard deviation

k k value, or tolerance limit factor, determined from the confidence level (95 %), probability content, p, and number of measurements, n, conducted. The k-value is found in Annex A

α Absolute error, in millilitres, used to define the upper and lower specification limits for a pre-set dose in absolute terms

β Relative error, as a percentage, used to define the upper and lower specification limits for a pre-set dose in relative terms

P_T The transition point volume, in millilitres, at which the upper and lower specification limits for V_{set} change from absolute terms to relative terms:

$P_T = (100 \times \alpha)/\beta$

V_{USL} Upper specification limit for a given V_{set}

V_{LSL} Lower specification limit for a given V_{set}

5 Requirements

5.1 General requirements

a) NFISs where the user is required to set the dose, shall provide an indication by visual means and at least one other mode (tactile or audible) of the dose setting action. Once set, the NFIS shall provide an indication of the dose that has been set. This information can be displayed in drug-specific units (e.g. millilitres, milligrams, international units) or in a unit of measure (e.g. number, letter, percentage) appropriate for the drug to be delivered.

b) NFIS where the manufacturer has set the dose shall indicate the dose on the NFIS or the system labelling, as appropriate.

c) The NFIS shall indicate, at least by visual means, that the device is ready for injection.

d) After the injection, the NFIS shall indicate, by visual or auditory or tactile means, that the intended dose has been expelled.

e) The state of the NFIS, when ready to deliver the dose, shall be visibly different from its state when the dose has been delivered. For multi-dose NFISs, the device shall be designed so it is impossible to deliver a second dose after delivery of the first dose without a second and different operation.

f) The NFIS shall be designed to prevent or to reduce the risk due to premature or inadvertent actuation of the device, in order to prevent or mitigate any subsequent injury that might result.

g) The materials used in the medicinal product or test fluid path (as appropriate) and any device component likely to be in direct or indirect contact with body tissues (at the injection site) shall be demonstrated to be biocompatible in accordance with ISO 10993-1 and other relevant parts of the ISO 10993 series.

h) NFISs with an exposed nozzle orifice, within reach of fingertips or environmental surfaces during preparation of the device for use or upon setting it down, shall be equipped with a method of reducing the possibility of contact of the orifice and nozzle face with environmental surfaces between the time of filling and the time of actual administration of the medicinal product.

i) NFISs that are intended for use on more than one patient shall be designed to avoid potential transfer of pathogens between patients and the safety of the system in this respect shall be demonstrated.

   Potential pathways for pathogen transfer to be considered may include transfer from the injection site back into the nozzle orifice, or back into an associated reservoir. They may also include splashback deposition of pathogens onto surfaces of the device likely to contact a subsequent injection site.

   For reusable NFISs, a documented and validated device cleaning and disinfection or sterilization process shall be demonstrated.

j) Components intended to be sterile shall be subjected to a validated sterilization process in accordance with applicable standards.

k) Claimed lifetime shall be determined by the manufacturer based on empirical testing. The claimed lifetime may be expressed either in terms of its total number of injections, or the period of time it may be used at specified expectations for the frequency of usage (i.e. injections per week, month or year). If the NFIS is designed to stop working after a limited time or number of operations, the total number of operations or time shall be adopted as the claimed lifetime.