INTERNATIONAL STANDARD

ISO 21649

First edition
2006-06-01

Needle-free injectors for medical use — Requirements and test methods

Injecteurs sans aiguille à usage médical — Exigences et méthodes d'essai

Reference number
ISO 21649:2006(E)

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Published in Switzerland

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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.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

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.

ISO 21649 was prepared by Technical Committee ISO/TC 84, *Devices for administration of medicinal products and intravascular catheters*.

Introduction

This International Standard applies to needle-free injectors primarily intended to administer medicinal products to humans. Because of the anticipated variation in the designs of such a broad array of devices, this International Standard is promulgated more as a “horizontal” rather than a “vertical” one. Thus, it will tend to specify 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 needle-free injector devices 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, shall fall under the authority of national governments or supranational agencies regulating the manufacture and marketing of medical devices and pharmaceutical products. Such standards are expected to be supplemented by additional requirements and may occasionally be superseded by such regulatory authorities. Despite certain advantages for intentional interchangeability for dose chambers designed for different needle-free injection systems, 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. This issue is left for future initiatives to build upon the standards promulgated herein.

The sampling plans for inspection selected for this International Standard are intended to verify the design, at a high confidence level, i.e., the manufacturer's ability to manufacture one “lot” of needle-free injectors, 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. the ISO 9000 series or ISO 13485.

Needle-free injectors for medical use — Requirements and test methods

1 Scope

This International Standard applies to safety and performance and testing requirements for single-use and multiple-use needle-free injection systems intended for human use in clinics and other medical settings and for personal use by patients.

The dose chamber of the injection system 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 also may be a permanent internal chamber designed to last through the claimed life of the device.

Excluded from this International Standard 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 referenced documents are indispensable for the application 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 3207:1975, *Statistical interpretation of data — Determination of a statistical tolerance interval*

ISO 3746:1995, *Acoustics — Determination of sound power levels of noise sources using sound pressure — Survey method using an enveloping measurement surface over a reflecting plane*

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

ISO 11201:1995, *Acoustics — Noise emitted by machinery and equipment — Measurement of emission sound pressure levels at a work station and at other specified positions — Engineering method in an essentially free field over a reflecting plane*

ISO 11202:1995, *Acoustics — Noise emitted by machinery and equipment — Measurement of emission sound pressure levels at a work station and at other specified positions — Survey method* in situ

ISO 11204:1995, *Acoustics — Noise emitted by machinery and equipment — Measurement of emission sound pressure levels at a work station and at other specified positions — Method requiring environmental corrections*

ISO 14155-1:2003, *Clinical investigation of medical devices for human subjects — Part 1: General requirements*

ISO 14155-2:2003, *Clinical investigation of medical devices for human subjects — Part 2: Clinical investigation plans*

ISO 14253-1:1998, *Geometrical Product Specifications (GPS) — Inspection by measurement of workpieces and measuring equipment — Part 1: Decision rules for proving conformance or non-conformance with specifications*

IEC 60068-2-27:1987, *Environmental testing — Part 2: Tests. Test Ea and guidance: Shock*

IEC 60068-2-30:2005, *Environmental testing — Part 2-30: Tests. Test Db and guidance: Damp heat, cyclic (12 h + 12 h cycle)*

IEC 60068-2-32:1975, *Environmental testing — Part 2: Tests. Test Ed: Free fall*

IEC 60068-2-64:1993, *Environmental testing — Part 2: Test methods — Test Fh: Vibration, broad-band random (digital control) and guidance*

IEC 60601-1-1:2000, *Medical electrical equipment — Part 1-1: General requirements for safety — Collateral standard: Safety requirements for medical electrical systems*

IEC 60721-3-7:2002, *Classification of environmental conditions — Part 3-7: Classification of groups of environmental parameters and their severities — Portable and non-stationary use*

IEC 61000-4-2:2001, *Electromagnetic compatibility (EMC) — Part 4-2: Testing and measurement techniques — Electrostatic discharge immunity test*

IEC 61000-4-3:2002, *Electromagnetic compatibility (EMC) — Part 4-3: Testing and measurement techniques — Radiated, radio-frequency, electromagnetic field immunity test*

IEC 61672-1:2002, *Electroacoustics — Sound level meters — Part 1: Specifications*

GUM:1995, *Guide to the Expression of Uncertainty in Measurement (GUM). BIPM, IEC, IFCC, ISO, IUPAC, IUPAP, OIML* — First edition 1993, corrected and reprinted 1995

3 Terms and definitions

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

3.1
intended dose
amount (volume or mass) of medicinal product intended to be ejected at one time

3.2
ejected dose
amount (volume or mass) of medicinal product ejected at one time

3.3
dose specification
variation of dose quantities (volume or mass) — and a statistical summation of same — which the needle-free injection system will eject for one or for a range of nominal dose quantities, as annunciated by the dose indicator read by typical users of the device

3.4
dose chamber
final enclosure which holds the pharmaceutical product and has direct contact with it just prior to its administration to the patient

3.5
dose indicator
component of a needle-free injection system showing the intended dose to be delivered

NOTE Depending on the device design, such indication may or may not be apparent before the dose chamber is filled.

3.6
filling device
integral component or components of, or separate or separable accessory(ies) to, a needle-free injector which acts or assists in the transfer of medicinal product between a reservoir and a dose chamber

NOTE Needle-free injection systems in which the dose chamber is or can be pre-filled by the manufacturer of the medicinal product may function without any such filling device. When a filling device is required, it may be as simple as an adapter providing an interface between medicinal reservoir and dose chamber, (e.g., using the piston and plunger of the latter to effect the transfer), or be as complicated as a device with internal channels to actively withdraw and insert the medicinal product from and to the respective containers.

3.7
injection mechanism
components of the needle-free injection system which are designated to harness, store, prevent (as in a "safety" latch), trigger, regulate, control and transfer to the dose chamber and/or its contained medicinal product the energies required for the injection to occur

NOTE This term is not used to refer to separate accessories which transfer energy into the needle-free injector but which are separated from the needle-free injector 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).

3.8
claimed lifetime
total number of ejections that a needle-free injection system, in normal use with recommended user maintenance and before manufacturer overhaul or refurbishment of parts, is expected to administer within its performance profile specified by the manufacturer

NOTE 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).

3.9
maximum and minimum dose
volumes, masses or number of units representing the largest and smallest quantities, which the manufacturer designates the needle-free injection system is capable of ejecting by one injection

3.10
reservoir
intermediate enclosure that holds and has contact with the medicinal product immediately prior to its transfer into the dose chamber

NOTE This container is often the vial or other enclosure filled with the medicinal product by the pharmaceutical manufacturer (and termed the "primary packaging" in that industry). It may 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. There may be no medicinal reservoir for those needle-free injection systems in which the dose chamber is pre-filled by the manufacturer of the medicinal product.

3.11
needle-free injection system
needle-free injector and its components and accessories that administer a medicinal product, without any part of the system penetrating the skin or mucous membranes

NOTE Such components and accessories may include:

— disposable or re-usable dose chambers;

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

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

— instructions and educational materials for end-users.

3.12
needle-free injector
device that administers 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

3.13
nozzle
component of an injector through which the medicinal product is ejected

NOTE The nozzle may or may not — depending on the device design — make physical contact with the skin or other membranes of the patient.

3.14
orifice
hole at the end of the nozzle, through which the medicinal product is expelled

3.15
performance profile
manufacturer-specified set of measurable and quantitative values and tolerance intervals which describes the proper functioning of a needle-free injection system

3.16
replicate
random sequence of V_{min}, V_{mid}, and V_{max}

3.17
unit container
customer packaging of an individual component or needle-free injection system

4 Symbols and abbreviated terms

V_{set} One of the 3 pre-set doses (expressed as a volume in millilitres) used in determining the uncertainty of dose for a given needle-free injector. V_{set} is defined as one of the following:

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 injector setting closest to ($V_{min} + V_{max}$)/2.

NOTE 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};

G_{meas} The gravimetric measurement value for a given V_{set};

ρ Mass density expressed in grams per millilitre;

p Probability content;

n Number of needle-free injectors required for a given test;

$\bar{x}$ The sample average (based on a random sample), an estimate of the population average:

$\bar{x} = \Sigma V_{meas}/n$;

s The sample standard deviation (based on a random sample), an estimate of the population standard deviation:

$$s = \sqrt{\frac{\sum \left(V_{meas} - \bar{x}\right)^2}{n-1}}$$

k Tolerance Limit Factor; determined from the confidence level, probability content, p, and the number of measurements, n, conducted at each dose setting;

TP The transition point in millilitres, the volume at which the definition of the upper and lower specification limit for V_{set} changes from absolute terms to relative terms:

TP = 0,2 ml;

USL Upper Specification Limit for a given V_{set};

LSL Lower Specification Limit for a given V_{set}.

5 Requirements

5.1 General requirements

When the needle-free injector is ready for injection, there is an indication to the user that the intended dose of medicinal product is present to be delivered. The needle-free injector shall indicate the dose to be delivered.

The needle-free injector shall indicate, at least by visual means, that the device is ready for injection.

After the injection, the needle-free injector shall indicate, by visual or auditory or tactile means, that the intended dose has been expelled.

The state of the needle-free injector, when ready to deliver the dose, shall be visibly different from its state when the dose has been delivered. For multi-dose needle-free injectors, 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.

The needle-free injector shall be designed to prevent or to reduce the risk of premature or inadvertent actuation of the device, and/or to prevent or mitigate any injury that might result.

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 ISO 10993.

Devices 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.

Needle-free devices that are intended for use on more than one patient shall be designed for, and shall have safety demonstrated with regard to, the potential transfer of pathogens between patients.

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

Needle-free injectors shall not produce sound which would exceed the current recommended exposure limits (REL) for occupational noise.

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 needle-free injector 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.

If power to the needle-free injector is provided by an external power supply (“mains”), then electrical safety shall be obtained through normative references to IEC 60601-1-1:2000. Needle-free injectors utilizing other sources of power shall reference applicable standards.

5.2 Noise requirements

If it is foreseeable that the device can be fired unintentionally in open air, the C-weighted peak emission sound pressure level, $L_{pC\ peak}$, produced by the needle-free injector shall not exceed 120 dB (for protection of the patient) when fired in open air.

If it is not foreseeable that the device can be fired unintentionally in open air, the C-weighted peak emission sound pressure level, $L_{pC\ peak}$, produced by the needle-free injector shall not exceed 130 dB (for protection of the patient) with the injection head against a surface which imitates actual use as defined by the manufacturer.

The A-weighted single event emission sound pressure level (SEL), $L_{pA,\ 1s}$ produced by the needle-free injector, with the injection head against a surface which imitates actual use as defined by the manufacturer, shall fulfil:

$$L_{pA,\ 1s} < 85 - 10 \log_{10} (N/28\ 800)$$

where N is the claimed maximum number of shots per 8 h period as declared by the manufacturer.

NOTE This requirement corresponds to $L_{EP,d} < 85$ dB.

Where the above sound pressure levels are exceeded, a warning shall be given in the instructions for use, see 8.3 p).

5.3 Dose specification requirements

The dose specification of the needle-free injector shall be determined by the procedures described in 6.4.1. The specification limits for the expelled liquid dose will be ± 0,01 ml for all doses of 0,2 ml or less. For all doses more than 0,2 ml, the specification limits of the expelled dose shall be ± 5 %.

For the situation where the dose specification limits above are not relevant to the intended therapeutic use, human clinical data shall be provided to substantiate the dose specification limits claimed. In the case of refillable devices this exception shall be indicated on the unit container (see 8.2.3) and in the instructions for use (see 8.3).

5.4 Uncertainty of measurements and conformance with specifications

The uncertainty of measurements shall be evaluated and expressed by the laboratory performing the test in accordance with Guide to the Expression of Uncertainty in Measurement (GUM).

The conformance with specification is proven in accordance with ISO 14253-1.

Conformance with specification is proven when the result of a measurement falls within the tolerance zone of the characteristic of a needle-free injector.

5.5 Performance profile requirements

5.5.1 There shall be an established performance profile.

5.5.2 The performance profile shall define the properties and tolerance intervals of the device required for consistent, reliable delivery of the medicinal product to the targeted tissues.

NOTE The performance profile and results may include one or more of the following parameters: pressure, force, volume, mass, velocity, time, distance, movement, depth or dispersion of penetration, and stream cross-section or silhouette, among others.

5.5.3 The performance profile of the needle-free injector shall be verified by clinical data from studies conducted in accordance with ISO 14155-1 and ISO 14155-2 and good clinical practice (GCP) using the same needle-free injector or a needle-free injector demonstrated to have an equivalent performance profile. The performance profile of a device shall be correlated to the desired clinical "end-point" of successfully delivering one or more representative drugs, vaccines or other medicinal products.

NOTE The performance profile is derived from tests that do not use human subjects (i.e. preclinical, e.g. bench procedures or laboratory animal studies) which in the development phase of the device have been correlated with high predictive value to human (clinical) studies. Such studies would have demonstrated successful delivery of the intended medication(s) to the target tissues, achieving therapeutic bioavailability or pharmacokinetics, or reaching another appropriate endpoint in humans. The purpose of the performance profile is to ensure that each new unit or batch will perform in an equivalent manner to the predicate device tested in clinical studies during its development and initial registration/licensure. With this "bridge" between physical or animal testing and prior demonstration of clinical effect, newly-manufactured devices — including those which may differ somewhat due to subsequent design refinements — are presumed to also successfully deliver the intended medication to humans if they satisfy the established performance profile.

5.5.4 Sufficient details of the test methodology shall be specified to permit independent verification of the performance profile.

NOTE Regulatory provisions may require the details of the test methodology to be made available to regulatory authorities so that the procedures can be evaluated and repeated by regulatory bodies.

5.6 Test requirements

5.6.1 Needle-free injectors subjected to standard, cool and hot atmospheres and after claimed lifetime testing

When tested in accordance with 6.2.2:

— the needle-free injectors shall have an uncertainty of dose within the limits specified in 5.3, when subjected to standard, cool and hot atmospheres;

— none of the needle-free injectors shall have visual defects after being subjected to standard, cool and hot atmospheres except for broken dose chambers that are obvious to the user;

— the needle-free injectors shall have a performance profile within the limits specified by the manufacturer after being subjected to standard, cool and hot atmospheres;