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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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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.

l) If the NFIS is powered by means other than manual effort, for example electricity, compressed gas or combustion, then the manufacturer shall ensure the safety of users and patients through risk assessment and by reference to appropriate standards. In the example of electrical power, this will include applicable parts of the IEC 60601-1 series. This will apply whether the power source provides energy for the injection mechanism or for other functions such as dose setting.

m) If any component intended to be removed from a NFIS fits entirely in any orientation into the small part cylinder shown in Figure 1, without compressing the component, then the NFIS shall be accompanied by an age warning (see Annex C).

Dimensions in millimetres

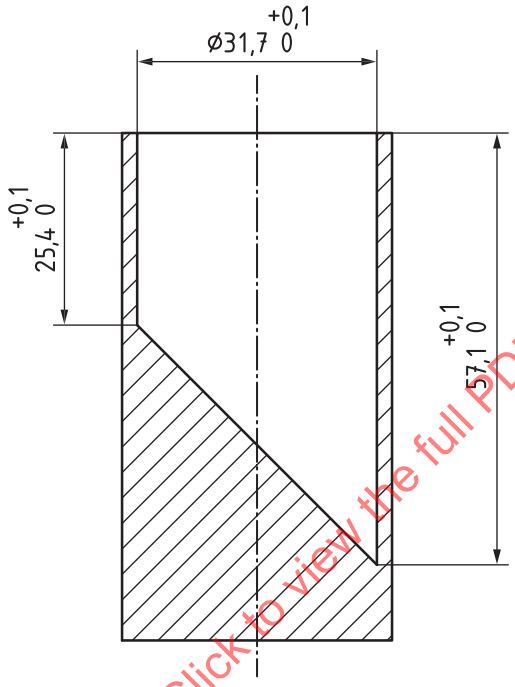


Figure 1 — Small part cylinder

NOTE The figure is reproduced from ISO 8124-1:2022, Figure 26.

5.2 Noise requirements

The C-weighted peak emission sound pressure level, $L_{pC\ peak}$, produced by the NFIS shall not exceed 120 dB (for protection of the patient) at a maximum distance of 500 mm from the main sound-emitting part of the NFIS. If, by risk assessment, it is determined that the NFIS will be used at a distance of less than 500 mm from the patient's or user's ear, then the distance at which the sound level will be measured shall be reduced accordingly.

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

$$L_{pA,\ 1s} < 80 - 10 \log_{10} (N/28\ 800)$$

where N is the maximum number of shots possible in an 8-hour period as declared by the manufacturer.

NOTE 1 This requirement corresponds to 8-hour A-weighted average sound pressure level < 80 dB(A).

If it is not possible to reduce sound pressure levels to those specified here, specific usage instructions and warnings shall be provided (for example use of hearing protection) to ensure that patients and

users are not exposed to sound pressure levels above those specified. This shall be supported by an appropriate risk assessment.

NOTE 2 Local regulations can require lower sound pressure exposure limits.

5.3 Dose accuracy specification requirements

The dose accuracy of the NFIS shall be determined by the procedures described in 6.3.1. The accuracy specification limits for the expelled liquid dose volume shall be:

α = ±0,01 ml (applicable to V_{set} <0,2 ml);

β = ±5 % (applicable to V_{set} >0,2 ml);

P_T is when V_{set} = 0,2 ml.

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

NOTE See Annex B for examples of accuracy limit calculations.

5.4 Usability engineering

A usability engineering program in accordance with IEC 62366-1 shall be applied, which shall include addressing use risks and tests and/or assessments throughout the development and as part of the design verification.

5.5 Risk approach

The manufacturer shall perform risk analysis, risk evaluation, risk control, evaluation of residual risk acceptability in accordance with ISO 14971:2019, Clauses 4 to 8.

Risk management tools shall be used to accomplish the following:

— identify functional objectives of the system in relation to the intended use of the NFIS;

— identify, establish and add requirements, specifications, methods or limits unique to each specific NIS (taking into account the medical condition for which the product is intended), when they are not provided in this document.

All additions, exclusions and modifications of requirements, specifications, methods or limits contained in or referenced in this document shall be documented and justified.

NOTE 1 For additional understanding about risk approach, see Introduction.

NOTE 2 Risk approach can include foreseeable “worst case” NFIS use-cases (e.g. NFIS regularly carried by user, versus being stored until immediately before use), conditions, requirements, or configurations.

5.6 Uncertainty of measurements and conformance with specifications

Uncertainty of measurement shall be evaluated and expressed.

NOTE 1 ISO/IEC Guide 98-3 (GUM) provides guidance on uncertainty of measurement.

In addition, 6.1 provides specific requirements for the repeatability and reproducibility of the test apparatus for the measurement of the performance profile of the NFIS.

Uncertainty of measurement shall be considered when establishing conformance of physical characteristics of the NFIS with specifications.

NOTE 2 ISO 14253-1 provides guidance on decision rules for proving conformity or nonconformity based on geometrical product specifications.

NOTE 3 The requirement to evaluate and express the uncertainty of measurement applies to measurements of physical characteristics of the NIS such as the performance profile, geometrical specifications, etc.

Specifications in this document of intervals for the magnitudes and/or quality of test conditions and preconditions (e.g. temperatures or vibration amplitudes) are not intended to include measurement uncertainty.

5.7 Performance profile requirements

5.7.1 There shall be an established performance profile.

5.7.2 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 can 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.

5.7.3 The performance profile of the needle-free injector shall be verified by clinical data from studies conducted in accordance with ISO 14155 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, were 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 can 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.

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

NOTE Regulatory provisions can 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.

5.8 Test requirements

5.8.1 NFISs subjected to standard, cool and hot atmospheres and after claimed lifetime testing (in-use conditions)

When tested in accordance with 6.2.2:

— the NFISs shall have a dose accuracy within the limits specified in 5.3, when subjected to standard, cool and hot atmospheres;

— none of the NFISs shall have visual defects after being subjected to standard, cool and hot atmospheres;

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

— none of the NFISs shall have visual defects after being subjected to claimed lifetime testing;

— the NFISs shall have a dose accuracy within the limits specified in 5.3 after being subjected to claimed lifetime testing;

— the NFISs shall have a performance profile within the limits specified by the manufacturer after being subjected to claimed lifetime testing.

NFISs with pre-filled non-replaceable dose chambers that have lower and/or higher acceptable operating temperatures than those specified in this document shall be subjected to the test at the extremes of the acceptable temperatures. These acceptable operating temperatures shall be stated in the instructions for use.

NFISs designed for a single actuation shall be excluded from claimed lifetime testing.

5.8.2 Dry heat storage - Preconditioning

When tested in accordance with 6.2.3:

— none of the NFISs shall have visual defects after being subjected to a dry heat storage atmosphere;

— the NFISs shall have a dose accuracy within the limits specified in 5.3, after being subjected to a dry heat storage atmosphere;

— the NFISs shall have a performance profile within the limits specified by the manufacturer after being subjected to a dry heat storage atmosphere.

NFISs with pre-filled non-replaceable dose chambers with a lower acceptable storage temperature shall be subjected to the preconditioning at a temperature no lower than the temperature specified in the instructions for use.

5.8.3 Damp heat storage – Preconditioning

When tested in accordance with 6.2.4:

— none of the NFISs shall have visual defects that might affect the safe operation after being subjected to a damp-heat storage atmosphere;

— the NFISs shall have a dose accuracy within the limits specified in 5.3, after being subjected to a damp-heat atmosphere;

— the NFISs shall have a performance profile within the limits specified by the manufacturer after being subjected to a damp-heat atmosphere.

NFISs with pre-filled non-replaceable dose chambers with a higher acceptable storage temperature shall be subjected to the preconditioning at a temperature no lower than the temperature specified in the instructions for use.

5.8.4 Cold storage - Preconditioning

When tested in accordance with 6.2.5:

— none of the NFISs shall have visual defects after being subjected to a cold storage atmosphere;

— the NFISs shall have a dose accuracy within the limits specified in 5.3, after being subjected to a cold storage atmosphere;

— the NFISs shall have a performance profile within the limits specified by the manufacturer after being subjected to a cold storage atmosphere.

NFISs with pre-filled non-replaceable dose chambers with a higher minimum acceptable storage temperature shall be subjected to preconditioning at a temperature no higher than the minimum acceptable temperature specified in the instructions for use.

5.8.5 Cyclical testing - Preconditioning

When tested in accordance with 6.2.6:

— none of the NFISs shall have visual defects after being subjected to a cyclical atmosphere;

— the NFISs shall have a dose accuracy within the limits specified in 5.3, after being subjected to a cyclical atmosphere;

— the NFISs shall have a performance profile within the limits specified by the manufacturer after being subjected to a cyclical atmosphere.

NFISs with a pre-filled non-replaceable dose chamber shall not be required to fulfil the requirements of this subclause.

5.8.6 Free fall - Preconditioning

When tested in accordance with 6.2.7:

— none of the NFISs with replaceable dose chambers shall have visual defects after being subjected to free fall except for broken dose chambers that are obvious to the user;

— none of the NFISs with non-replaceable dose chambers shall have visual defects after being subjected to free fall except for broken dose chambers that are obvious to the user;

— the NFISs shall have a dose accuracy within the limits specified in 5.3, after being subjected to free fall;

— the NFISs shall have a performance profile within the limits specified by the manufacturer after being subjected to free fall.

5.8.7 Vibration and shock – Preconditioning

When tested in accordance with 6.2.8:

— none of the NFISs shall have visual defects after being subjected to vibration and shock;

— the NFISs shall have a dose accuracy within the limits specified in 5.3, after being subjected to vibration and shock;

— the NFISs shall have a performance profile within the limits specified by the manufacturer after being subjected to vibration and shock.

NFISs with limited conditions for vibration and shock shall be subjected to the test at the acceptable conditions, and these acceptable conditions shall be stated in the instructions for use.

5.8.8 Transport – Preconditioning

Subject a new set of NFISs (in final packaging) to transportation consistent with the conditions under which the finished product is intended to be shipped.

Standards method for these types of studies can include ASTM D4169 and ISTA Procedures, or actual shipment of the product before testing.

Where transportation studies are considered worst case and not representative of normal shipping, it is not intended that they be combined with any other preconditioning testing.

5.8.9 NFISs with electrical components subjected to electromagnetic compatibility (EMC)

5.8.9.1 General

The requirements given in 5.8.9.2 and 5.8.9.3 are requirements substituting those specified in IEC 60601-1-2 as the latter International Standard covers requirements for electro-medical appliances in general only, and it does not address specific devices such as NFISs.

NOTE 1 The tests specified in 5.8.9.2 and 5.8.9.3 are based on the requirements given in the collateral standard IEC 60601-1-2. In that International Standard, EMC references are given to the IEC 61000-4-1 (IEC 61000-4-2:2008 and IEC 61000-4-3:2020 in particular. The span of the sweep in that standard covers all the frequencies of mobile communication systems.

NOTE 2 These requirements apply only to NFISs with electronic components.

5.8.9.2 Electrostatic discharge

When tested in accordance with 6.2.9:

— none of the NFISs shall have visual defects after being subjected to electrostatic discharge levels;

— the NFISs shall have a dose accuracy within the limits specified in 5.3, after being subjected to electrostatic discharge levels;

— the NFISs shall have a performance profile within the limits specified by the manufacturer after being subjected to electrostatic discharge levels.

5.8.9.3 Radiated radio frequency (RF) fields

When tested in accordance with 6.2.9:

— none of the NFISs shall exhibit erroneous indications during the radio frequency sweep;

— none of the NFISs shall have visual defects after being subjected to the radiated frequency fields;

— the NFISs shall have a dose accuracy within the limits specified in 5.3, after being subjected to radiated radio frequency fields;

— the NFISs shall have a performance profile within the limits specified by the manufacturer after radiated radio frequency fields.

5.8.10 Water and dust resistance

When tested in accordance with 6.2.11:

— The NFIS shall meet the requirements of IP55 in accordance with IEC 60529 unless the instructions for use specify a more challenging ingress protection level.

— the NFISs shall have a performance profile within the limits specified by the manufacturer after being subjected to water and dust intrusion testing.

5.8.11 Auto-disable feature

When tested in accordance with 6.2.12:

— the dose chamber shall be passively and automatically rendered unusable after delivery of the intended dose.

6 Test methods

6.1 General

Each NFIS shall provide only one replicate to the pool of data from which the dose accuracy is calculated.

For a variable dose NFIS, each of the required dose sizes (i.e. V_{min}, V_{mid} and V_{max}) shall be evaluated separately in calculating dose accuracy. A single NFIS and dose chamber can be used to evaluate one V_{min}, V_{mid} and V_{max} dose for a given test.

NOTE 1 Using one dose of each dose size from each NFIS/dose chamber combination and randomizing the sampling sequencing of different dose volumes ensures both inter- and intra-device variability are captured in the measurement.

For a fixed-dose NFIS holding multiple doses, only one dose from each NFIS and dose chamber can be used in calculating dose accuracy. The dose that is used should be sequenced for each NFIS/dose chamber combination. (e.g. for a dose chamber that holds 5 doses, the first dose should be used from the first NFIS/dose chamber combination, the second dose from the second NFIS/dose chamber combination, the third dose from the third NFIS/dose chamber combination, repeating and starting over at the first dose after the fifth NFIS/dose chamber combination).

NOTE 2 Taking one dose from each NFIS/dose chamber combination and sequencing the dose ensures that both inter- and intra-device variability are captured in the measurement.

NOTE 3 To satisfy the different testing requirements of Clause 5 and minimize the number of samples needed to complete the testing, the same group of NFISs can be used for the different tests specified in 6.2.2 to 6.2.9. It is not required to perform test evaluations (dose accuracy, performance profile and visual inspection) specified in 6.2.2 to 6.2.9 after each preconditioning. In such cases, the test evaluations can be performed after the last preconditioning to which the NFIS samples have been subjected. If these final test evaluations result in a failure, the manufacturer may be unable to determine which preconditioning or sequence of preconditioning resulted in the failure.

Unless otherwise specified, all tests and test evaluations shall be performed at standard atmosphere conditions (as defined in 6.2.2).

The NFIS is prepared in accordance with the instructions for use.

Any suitable test system can be used for the measurement of dose volume delivered from the NFIS, when the required accuracy (calibration) and precision (Gauge R&R) can be obtained. The repeatability and reproducibility (Gauge R&R) of the test apparatus shall be no greater than 20 % of the allowed tolerance range for any given measurement. For one-sided tolerances, an interval shall be established by adding the missing end-point (i.e. not as a specification limit). For destructive test measurements, the Gauge R&R shall be no greater than 30 % of the allowed tolerance range. At a minimum, the Gauge R&R should cover ±2 standard deviations (thereby covering approximately 95 % of the variation).

NOTE 4 An extra end-point for one-sided tolerances can be based on physical limitations of the NFIS or the measurement system (e.g. noting that a duration of time cannot be negative), or be based on the distribution of the measurement results (e.g. setting the end-point six times the standard deviation from the mean).

For attributive methods, an attribute Gauge R&R shall be used. The total effectiveness:

$$E = n_{correct}/n_{total}$$

shall be at least 0,90 (90 %), and the probability of a false acceptance:

$$P(FA) = n_{FA}/n_{reject}$$

shall be no more than 0,025 (2,5 %).

where:

n_{total} is the total number of assessments made;

$n_{correct}$ is the number of correct assessments made;

n_{FA} is the number of rejectable items (i.e. items that should be rejected), but which have been accepted (false acceptance);

n_{reject} is the total number of items that should have been rejected.

EXAMPLE A measurement system with a measurement specification limit of ±0,01 ml (range of 0,02 ml) comes out of the Gauge R&R with a precision/tolerance ratio of 20 %, which means that the Gauge R&R (4 standard uncertainties) equals 0,02 ml/5 = 0,004 ml. The uncertainty of the measurement is ±2 standard deviations (GUM), which equals 0,002 ml.

The NFIS shall be operated either manually or automatically, in a way that simulates operation by the end-user, as described in the instructions for use.

6.2 Test procedures

6.2.1 General

Using the probability content levels of 0,950 (95 %) and 0,975 (97,5 %), the two-sided statistical tolerance interval for a given test and V_{set} can be calculated.

The manufacturer shall select a number of NFISs to test, denoted n, appropriate for the tests specified in 6.2.2 to 6.2.9. The number of NFISs shall not be fewer than 20 for these tests.

Table 1 and Table 2 show the confidence and probability content requirements for dose accuracy and test requirements.

Table 1 — Confidence and probability content requirements for dose accuracy

Minimum confidence	Minimum probability content, p	Examples of number of NFISs to test, n	Corresponding target, k for each n (from Annex A)
0,95	(p = 0,975)	60 30 25 20	2,670 2,921 3,015 3,154
0,95	(p = 0,950)	60 30 25 20	2,335 2,555 2,638 2,760
Number of NFISs n in are provided as an example.			

NOTE The sampling plans for inspection selected for this document are intended to verify the design at a high confidence level. The sampling plan does not replace the more general manufacturing quality systems, including lot release, which appear in International Standards on quality systems, e.g. ISO 9001 or ISO 13485.

Table 2 — Test requirements for NFIS

Confidence	Content	Subclause	Descriptions	Dose chamber replaceable	Pre-filled dose chamber non-replaceable	Empty dose chamber non-replaceable
0,95	(p = 0,975)	5.8.1[a]	Standard, cool, hot, lifetime	x	x[b]	x
		5.8.2	Dry heat storage	x	x[c]	x
		5.8.3	damp heat storage	x	x[c]	x
		5.8.4	Cold storage	x	x[d]	x
0,95	(p = 0,975)	5.8.5	Cyclical atmosphere	x	—	x
		5.8.6[e]	Free fall	x	x	x
		5.8.7[f]	Vibration, shock	x	x	x
		5.8.8	Transport	x	x	x
		5.8.9.2[g]	Electrostatic	x	x	x
		5.8.9.3[g]	RF fields	x	x	x

[a] Single-use NFISs are excluded from claimed lifetime testing. In addition, a new single-use injector shall be used for all of the other tests in 6.2.2.

[b] NFISs with pre-filled non-replaceable dose chambers that claim different acceptable operating temperatures than specified in this document shall be subjected to the test at maximum acceptable temperature, which shall be stated in the instructions for use.

[c] NFISs with pre-filled non-replaceable dose chambers with a lower acceptable storage temperature shall be subjected to the test at maximum acceptable temperature.

[d] NFISs with pre-filled non-replaceable dose chambers with a higher acceptable storage temperature shall be subjected to the test at lowest acceptable temperature.

[e] When free fall testing NFISs with non-replaceable dose chambers, a sufficient number of NFISs shall be tested to ensure that n NFISs are available for dose accuracy testing.

[f] NFISs that cannot satisfy the requirements of vibration and shock testing described in this document shall be subjected to such testing at the acceptable conditions, which shall be stated in the instructions for use.

[g] NFISs without electronic components shall be exempt from electromagnetic compatibility testing.

6.2.2 NFISs subjected to standard, cool and hot atmospheres and claimed lifetime test

6.2.2.1 Standard atmosphere test

Subject n new NFISs to storage for at least 4 h to the standard atmosphere specified as follows;

— Temperature: from 18 °C to 28 °C;

— Relative humidity: from 25 % RH to 75 % RH

The n new NFISs shall be tested for dose accuracy in accordance with 6.3.1.

Measure the performance profile for the n NFISs and confirm that the profile meets the manufacturer's specification.

6.2.2.2 Cool atmosphere test

— Reusable NFISs with replaceable containers: Subject the same NFISs to storage for at least 4 h in a test chamber maintained at the following specified cool atmosphere;

— NFISs with non-replaceable containers which is integrated, or user assembled: Subject n new NFISs to storage for at least 4 h in a test chamber maintained at the following specified cool atmosphere;

  — Temperature: 5 °C ± 3 °C.

Determine the dose accuracy at these conditions in accordance with 6.3.1:

Test execution shall ensure the NFIS is acclimatized to the atmospheric conditions specified above during testing. This may be achieved by testing at these atmospheric conditions or by testing at standard atmosphere without time for acclimatization after removal from the test chamber. Testing at standard atmosphere shall be supported by a rationale, and the time from removing the NFIS until the end of the test shall be as short as possible.

Determine the performance profile at these conditions in accordance with the manufacturer's specification.

6.2.2.3 Hot atmosphere test

— Reusable NFISs with replaceable containers: Subject the same NFISs to storage for at least 4 h in a test chamber maintained at the following specified hot atmosphere;

— NFISs with non-replaceable containers which is integrated, or user assembled: Subject *n* new NFISs to storage for at least 4 h in a test chamber maintained at the following specified hot atmosphere;

  — Temperature: 40 °C ± 2 °C;

  — Relative humidity: 50 % RH ± 10 % RH.

Determine the dose accuracy at these conditions in accordance with 6.3.1:

Test execution shall ensure the NFIS is acclimatized to the atmospheric conditions specified above during testing. This may be achieved by testing at these atmospheric conditions or by testing at standard atmosphere without time for acclimatization after removal from the test chamber. Testing at standard atmosphere shall be supported by a rationale, and the time from removing the NFIS until the end of the test shall be as short as possible.

Determine the performance profile at these conditions in accordance with the manufacturer's specification.

6.2.2.4 Lifetime test

6.2.2.4.1 Lifetime test (reusable NFISs with replaceable containers)

Determine the claimed lifetime of the NFIS in compliant use before overhaul/refurbishment of parts.

Subject the same NFISs above, to the standard atmosphere as specified above.

NOTE 1 The manufacturer can decide to select a smaller *n* for the lifetime testing than that chosen for the previous tests. However, a corresponding target *k* would result from this different *n*.

Subject *n* NFISs tested above to the claimed lifetime testing (simulate manual use in accordance with the instructions for use) as follows:

a) remove the cap permanently if it has no influence on the safety of the NFIS;

b) insert or fill the dose chamber;

c) prepare the NFIS for injection;

d) expel a dose of an amount which is anticipated to represent the worst case;

e) repeat b) to d) until 1,5 × the number of injection strokes of the claimed lifetime (in accordance with the manufacturers product file) is reached.

NOTE 2 Recommended user-maintenance tasks, e.g. lubrication or replacement of “o-rings” or other user-replaceable components, can be performed at their recommended intervals during the lifetime testing.

Visually inspect the NFISs in accordance with 6.3.2.

If the dose chamber is broken to the extent that it is obvious to the user, replace the dose chamber. If the dose chamber is non-replaceable and is broken to the extent that is obvious to the user, exclude the NFIS from further testing.

Determine the dose accuracy in accordance with 6.3.1.

Determine the performance profile in accordance with the manufacturer's specification.

6.2.2.4.2 Lifetime test (NFISs with non-replaceable containers which is integrated, or user assembled)

Subject *n* NFISs to storage at standard atmosphere for a time equal to the claimed expiration of the injectors.

Determine the dose accuracy at these conditions in accordance with 6.3.1.

Determine the performance profile at these conditions in accordance with the manufacturer's specification.

Testing can be done after accelerated aging per ASTM F1980, which then shall be confirmed with real time aging.

6.2.3 NFISs subjected to dry heat storage atmosphere

Subject *n* new NFISs to the dry heat storage atmosphere. The NFISs shall be placed in a test chamber for at least 96 h in the following dry heat atmosphere:

— Temperature: 70 °C ± 2 °C;

— Relative humidity: 50 % RH ± 10 % RH.

Visually inspect the NFISs in accordance with 6.3.2. If the dose chamber is broken to an extent that is obvious to the user, replace the dose chamber. If the dose chamber is non-replaceable and is broken to an extent that is obvious to the user, exclude the NFIS from further testing.

Subject the remaining NFISs to the standard atmosphere specified in 6.2.2.

Determine the dose accuracy in accordance with 6.3.1.

Determine the performance profile in accordance with the manufacturer's specification.

6.2.4 NFISs subjected to damp-heat storage atmosphere

— Reusable NFISs with replaceable containers: Subject the same NFISs to storage for at least 4 h in a test chamber maintained at the following specified damp heat atmosphere;

— NFISs with non-replaceable containers which is integrated, or user assembled: Subject *n* new NFISs to storage for at least 4 h in a test chamber maintained at the following specified damp heat atmosphere;

  — Temperature: 40 °C ± 2 °C;

  — Relative humidity: 93 % RH ± 5 % RH.

Determine the dose accuracy at these conditions in accordance with 6.3.1.

Test execution shall ensure the NFIS is acclimatized to the atmospheric conditions specified above during testing. This may be achieved by testing at these atmospheric conditions or by testing at standard atmosphere without time for acclimatization after removal from the test chamber. Testing at

standard atmosphere shall be supported by a rationale, and the time from removing the NFIS until the end of the test shall be as short as possible.

Determine the performance profile at these conditions in accordance with the manufacturer's specification.

6.2.5 NFISs subjected to cold storage atmosphere

Subject *n* new NFISs to the cold storage atmosphere. The NFISs shall be placed in a test chamber for at least 96 h in the following cold atmosphere:

— Temperature: −40 °C ± 3 °C.

Visually inspect the NFISs in accordance with 6.3.2. If the dose chamber is broken to an extent that is obvious to the user, the NFIS has failed.

Subject the remaining NFISs to the standard atmosphere specified in 6.2.2.

Determine the dose accuracy in accordance with 6.3.1.

6.2.6 NFISs subjected to a cyclical atmosphere

Subject *n* new NFISs to the cyclical atmosphere.

The NFISs shall be placed in a test chamber. Conditioning in accordance with IEC 60068-2-30 is carried out as follows:

— Variant 1 [see IEC 60068-2-30:2005, Figure 2 a)];

— Upper temperature: 55 °C ± 2 °C;

— cycles.

Visually inspect the NFISs in accordance with 6.3.2. If the dose chamber is broken to an extent that is obvious to the user, replace the dose chamber. If the dose chamber is non-replaceable and is broken to an extent that is obvious to the user, exclude the NFIS from further testing.

Subject the remaining NFISs to the standard atmosphere specified in 6.2.2.

Determine the dose accuracy in accordance with 6.3.1.

Determine the performance profile in accordance with the manufacturer's specification.

6.2.7 NFISs subjected to free fall

6.2.7.1 General

Unpack and prepare the NFISs according to the instructions for use with a new dose chamber. When an injector is part of a larger system, only the injector shall be tested. Coupled holders (glass), containing medicinal products, can be removed.

The free fall test shall be performed using a free fall system as specified in IEC 60068-2-31.

The test surface shall be smooth, hard, rigid and made of steel of 3 mm thickness backed by wood of between 10 mm and 19 mm thickness.

6.2.7.2 NFISs with replaceable dose chamber

Subject new NFISs to the standard atmosphere specified in 6.2.2 and continue as described below.

Fill the dose chamber and put on the cap.

Drop each NFIS 3 times by free fall in accordance with the conditions specified in IEC 60721-3-7:1995+AMD1:1996, Class 7M3, from one of the following heights:

— 1 000 mm for needle-free injectors with a mass of less than 1 kg;

— 500 mm for needle-free injectors with a mass of more than 1 kg and less than 10 kg;

— 250 mm for needle-free injectors with a mass of more than 10 kg;

on to the test surface, once horizontally and twice vertically, the NFIS being rotated 180° between the 2 vertical drops. The NFIS shall be dropped in a non-turbulent way.

If a dose chamber breaks such that it is obvious to the user, replace the dose chamber and continue until all 3 drops have been performed.

Visually inspect the NFISs in accordance with 6.3.2. If the dose chamber is broken to an extent that is obvious to the user, replace the dose chamber.

Determine the dose accuracy in accordance with 6.3.1.

Determine the performance profile in accordance with the manufacturer's specification.

6.2.7.3 NFISs with non-replaceable dose chamber

Subject new NFISs to the standard atmosphere specified in 6.2.2 and continue as described below.

Fill the dose chamber and put on the cap.

Drop each NFIS 3 times by free fall in accordance with the conditions specified in IEC 60721-3-7:1995+AMD1:1996, Class 7M3, from one of the following heights:

— 1 000 mm for NFISs with a mass less than 1 kg;

— 500 mm for NFISs with a mass more than 1 kg and less than 10 kg;

— 250 mm for NFISs with a mass more than 10 kg;

on to the test surface, once horizontally and twice vertically, the NFIS being rotated 180° between the 2 vertical drops. The NFIS shall be dropped in a non-turbulent way.

NOTE This preconditioning is to simulate accidental dropping of the NFIS by the operator. It is done in conformity with IEC 60068-2-31. The height at which the NFIS can be dropped has been differentiated to adjust the difference in the force of impact caused by the increase in mass or weight. However, manufacturers can use their risk assessments to assure that the height chosen is appropriate for their NFISs.

Visually inspect the NFISs in accordance with 6.3.2. If the dose chamber is broken to an extent that is obvious to the user, exclude the NFIS from further testing.

Determine the dose accuracy of *n* NFISs.

Determine the performance profile of *n* NFISs, in accordance with the manufacturer's specification.

6.2.8 NFISs subjected to vibration and shock

Place the NFISs in a safety case or pouch for transport according to the instructions for use. When an injector is part of a larger system, the whole system shall be tested. Coupled holders (glass), containing medicinal products, can be removed. Commence the test as follows:

Subject the NFISs to vibration in accordance with IEC 60068-2-64.

Subject the NFISs to the conditions specified in IEC 60721-3-7:1995+AMD1:1996, Class 7M3, as follows:

— acceleration spectral mass density 3 m^2/s^3, frequency interval 10 Hz to 200 Hz;

— acceleration spectral mass density 1 m^2/s^3, frequency interval 200 Hz to 500 Hz;

— vibrate the NFISs in a vertical direction and in two other directions perpendicular to one another in a horizontal plane.

The vibration time shall be 1 h.

NFISs that cannot satisfy the requirements of vibration and shock testing described in this document shall be subjected to such testing at the acceptable conditions, which shall be stated in the instructions for use.

NOTE 1 For clarification: The test described above is applicable to electrical and non-electrical devices (there are no other vibration standards available for non-electrical devices). IEC 60721-3-7 specifies requirements for portable devices. Class 7M3 is selected because its description of transportation of the NFIS.

NOTE 2 IEC 60068-2-64 describes the test equipment for the vibration test.

Subject the NFISs to the shock test in accordance with IEC 60068-2-27.

Subject the NFISs to the conditions specified in IEC 60721-3-7:1995+AMD1:1996, Class 7M3, as follows:

— to a shock response spectrum Type I: 300 m/s^2;

— to a shock response spectrum Type II: 1 000 m/s^2.

The number of shocks shall be 50 positive shocks and 50 negative shocks.

For intensive transportation of equipment over heavy surfaces, the Type I shock test should be over a number of 100 shocks positive and 100 negative shocks.

NOTE 3 For clarification: the test described above is applicable to electrical and non-electrical devices (there are no other shock standards available for non-electrical devices).

IEC 60721-3-7 specifies requirements for portable devices; Class 7M3 is selected because its description of transportation of the device; IEC 60068-2-27 describes the test equipment for the shock test; the shock response test Type I represents transport of the device in its packaging; the shock response test Type II represents the device in use (without packaging).

Visually inspect the NFISs in accordance with 6.3.2.

— For NFISs with replaceable dose chambers, if the dose chamber is broken to an extent that is obvious to the user, replace the dose chamber.

— For NFISs with non-replaceable dose chambers, if the dose chamber is broken to an extent that is obvious to the user, exclude the NFIS from further testing.

Determine the dose accuracy in accordance with 6.3.1.

Determine the performance profile in accordance with the manufacturer's specification.

6.2.9 NFISs with electrical components subjected to electromagnetic compatibility (EMC) testing

Test the NFISs for exposure to electrostatic discharge and radiated fields (RF) as follows.

Place *n* NFISs with the dose chambers on a metal reference plane as specified in IEC 61000-4-2:2008.

Apply contact discharges of (±2, ±4 and ±8) kV to conductive accessible parts and coupling planes.

Apply air discharges of (±8, ±10, ±12 and ±15) kV to non-conductive accessible parts.

The number of discharges at each level and polarity shall be 10, with a time interval of 1 s between the individual discharges.

Test the same NFISs in accordance with IEC 61000-4-3:2020 (TEM cells or GREM cells may be used as described in IEC 61000-4-3:2020, Annexes G and K).

As stated in IEC 61000-4-3:2020, the requirement for field uniformity shall be fulfilled in the area corresponding to the unit under test.

During emission test, radio frequency, and power magnetic field immunity tests, the NFIS shall be exercised simulating the intended use in the worst-case scenario identified as required by 5.5.

Special hardware or software might be needed to perform the emission and immunity tests. If so, this should be documented in the test plan and shall be documented in the test report.

During exposure to electrostatic discharge test, the NFIS may remain in power ON or OFF condition, whichever is deemed worst-case. Conformance is checked by inspection of the test report and the risk management file.

Test the same NFISs at the 10 V/m level (unmodulated carrier) in the frequency range of (26 to 2 000) MHz.

The test signal shall be amplitude modulated; modulation shall be with 1 kHz sinusoidal and to a modulation depth of 80 %.

Perform the test in each of the three axes of the NFIS.

Visually inspect the NFISs in accordance with 6.3.2. If the dose chamber is broken to an extent that is obvious to the user, replace the dose chamber.

Determine the dose accuracy in accordance with 6.3.1.

Determine the performance profile in accordance with the manufacturer's specification.

6.2.10 Noise testing

6.2.10.1 Environment for testing noise

Any environment that meets the qualification requirements of ISO 3746:2010, Annex A may be used.

NOTE In practice, this means a normally furnished room with a volume exceeding 30 m^3.

6.2.10.2 Instrumentation

The instrumentation system, including the microphone and cable, shall meet the requirements of a type 1 or type 2 instrument specified in IEC 61672-1. When measuring high peak emission sound pressure levels, the microphone and the entire instrumentation system shall have the capability of handling linear peak levels exceeding the C-weighted peak levels by at least 10 dB.

NOTE If ISO 11201 is used, a type 1 instrument is required.

6.2.10.3 Measurement procedure

The emission sound pressure levels at the specified positions around the NFIS shall be tested in accordance with ISO 11202 and ISO 11204, which are the survey methods. In case of ambiguity of which survey method should be used, the methods covered in ISO 11201 shall be used.

Two measurements shall be made, as follows:

$L_{pC\ peak}$ – the highest value recorded at any of the microphone positions for all events;

$L_{pA,\ 1s}$ –the sound level of a single event (operation of the NFIS) over one second. This is reported as the logarithmic mean of all measurements made from all microphone positions for a NFIS.

Use six microphone positions around the NFIS as shown in Figure 2, each at the distance determined by risk assessment (see 5.2) or a maximum of 500 mm from the origin of the measuring coordinate system. Place the main sound emitting part of the NFIS at the origin in its normal operating orientation in such a way that the main axis of the NFIS coincides with one axis of the measuring system. The NFIS shall be supported such that the sound emitted from the NFIS can reach the microphone position unimpeded.

For measurement of $L_{pA,1s}$, the NFIS shall be tested with the injection head against a surface that represents actual use as defined by the manufacturer. This surface should be as small as possible in order not to impede sound reaching any microphone position.

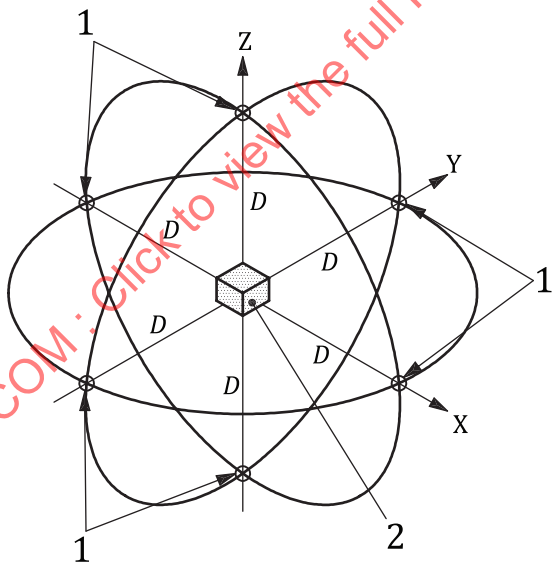
If, following a risk assessment, it is determined that the NFIS can be fired unintentionally in open air (not against skin or a surface representing actual use), then measurement of $L_{pC\ peak}$ shall be conducted without any surface representing actual use. Otherwise, measurement of $L_{pC\ peak}$ shall be conducted as for $L_{pA,\ 1s}$. In such cases, it is acceptable to make both measurements at the same time.

For each microphone position, make at least 3 measurements of $L_{pC\ peak}$ and at least 3 measurements of $L_{pA,1s}$. It is acceptable to make measurements of a single event at different positions by using multiple microphones.

Record the results as follows:

$L_{pC\ peak}$ – the highest value recorded at any of the microphone positions for all events;

$L_{pA,1s}$ – the logarithmic mean of all individual measurements of $L_{pA,1s}$.



Key

1 microphone

2 NFIS

D distance from origin to microphone position

Figure 2 — Microphone positions

6.2.11 Water and dust resistance

The injector shall resist exposure to rain or otherwise accidental exposure to water and dust.

Penetration shall not be less than rating IP55 per IEC 60529.

NFISs shall be tested in its worst-case use configuration.

Following testing, visually inspect the NFISs in accordance with 6.3.2.

Determine the performance profile in accordance with the manufacturer's specification.

Confirm the instructions for use indicate that the NFIS is resistant to short duration exposure to water.

6.2.12 Auto-disable feature

The dose chamber shall be passively and automatically rendered unusable after delivery of the intended dose.

The timing and method of the activation of the auto-disable feature may vary by design. It shall not be possible to intentionally or inadvertently re-use the dose chamber under the normal conditions of use.

NFISs shall meet the test requirements given in ISO 7886-3:2020, 13.4.

6.3 Test evaluations

6.3.1 Dose accuracy

6.3.1.1 General

The substance to be tested for dose accuracy assessment shall be either the medicinal product intended to be used with the NFIS, or a representative substance of appropriate viscosity, mass density or other applicable properties. NFISs not labelled to inject a specific medicinal product shall be tested across a representative range of substances described by the aforementioned physical properties.

Dose accuracy is determined by selecting and testing a number of NFISs. The number of NFISs depends upon the dose chamber and accuracy requirements for a given test. Assuming that the test results are normally distributed and that each measurement is independent, the following method enables accuracy result to be used as the basis for determining a statistical tolerance interval for 3 dose settings (the minimum, midpoint and maximum dose settings for a given NFIS), i.e. an interval such that there is a fixed probability (confidence level) that the interval will contain at least a proportion (p, probability content) of the true population from which the sample is taken. The statistical tolerance interval is two-sided, and the limits of the interval are called “statistical tolerance limits” or “natural limits of the process”.

To pass the requirement of dose accuracy, there shall be a 95 % confidence that at least p of all doses delivered will fall between the proposed upper and lower specification limits for the 3 dose settings.

The two-sided statistical tolerance interval is calculated using the average ($\bar{x}$) plus or minus the standard deviation of the sample values, s, multiplied by a tolerance limit factor, k:

$$\text{The two-sided statistical tolerance} = \bar{x} \pm (k \times s)$$

The factor, k, is determined based upon the confidence level (95 %), probability content, p, and the number of measurements, n, taken for each of the 3 dose settings. Annex A lists the tolerance limit factors for the construction of two-sided statistical tolerance intervals when the true population mean and standard deviation are not known. Annex A contains a more comprehensive two-sided tolerance limit for the 95 % confidence level.

6.3.1.2 Accuracy assessment

If $V_{set} \leq P_T$, then:

$$V_{USL} = V_{set} + 0{,}01 \text{ ml};$$

$V_{LSL} = V_{set} - 0{,}01$ ml.

If $V_{set} > P_T$, then:

$V_{USL} = V_{set} + (5 \times V_{set})/100$;

$V_{LSL} = V_{set} - (5 \times V_{set})/100$.

A NFIS population satisfies the requirements when, for a given V_{set}, the following expressions are fulfilled:

$\bar{x} + (k \times s) \leq V_{USL}$;

$\bar{x} - (k \times s) \geq V_{LSL}$.

See example in Annex D.

6.3.1.3 Gravimetric conversion

All doses (V_{set} or G_{set}) delivered are recorded gravimetrically (G_{meas}, expressed in grams). For solution-based systems, these recordings are converted to volumes (V_{meas}) by using the mass density (ρ, expressed in grams per millilitre) for the test fluid. The following equation can be used to convert gravimetric measurements to volumetric:

$V_{meas} = G_{meas} / \rho$

6.3.2 Inspection

6.3.2.1 General

While there are no specific statistical requirements (i.e. p-content and confidence level) for the inspections described in this clause, these inspections shall result in zero failures.

6.3.2.2 Legibility of markings

Visually inspect the NFIS using normal or corrected-to-normal vision, and environmental lighting conditions of ≤100 lx, and from one reading distance of between 30 cm and 70 cm. This inspection shall check that any marking on the NFIS (e.g. dose setting indication) shall remain visible and legible. This requirement does not apply to regulatory labelling on the NFIS or cartridge or unit container.

Visually inspect the performance (e.g. stored data, settings, dose or indications) of each NFIS that has electronic components.

NOTE 1 The legibility of markings inspection is supposed to ensure that NFIS users are able to read the markings under real-life conditions (e.g. limited light intensity) whereas the inspection for defects is intended to detect defects during design verification.

NOTE 2 The lighting levels chosen for this subclause were the lowest levels listed in ISO 8995-1, and depict ambient lighting levels that are likely to be seen in private homes or in the entrance halls, rest rooms or corridors of public spaces (e.g. hotels or hospitals). This level is chosen as representative of what patients – users of these hand-held, portable NFISs – might be expected to encounter as they look to read markings on these devices. Other lighting levels might be appropriate based on the intended use of the NFIS. These levels might be different from levels specified in earlier publications of this document and other international standards.

6.3.2.3 Freedom from defects

Visually inspect each NFIS for defects using normal, or corrected-to-normal vision and environmental lighting conditions of ≥750 lx, and from one reading distance of between 30 and 70 cm. Defects in electronic parts are permitted if the defect is obvious to the user and does not compromise NFIS safety.

The inspection should in particular include checking for defects such as:

— displaced parts;

— cracks in the body and/or component of the NFIS that might impact safe functioning;

— for NFISs with replaceable batteries, the battery compartment failing to remain closed;

— compromised assembly bonds, joints and alignments between the different parts of the body of the NFIS, which might impact safe functioning;

— cracked containers or loss of contents, other than containers that have been excluded for damage obvious to the user in line with 5.8.6.

NOTE The lighting levels chosen for this subclause were the lighting levels listed in ISO 8995-1 expected to be seen in inspection areas in the chemical, plastics or rubber industry – and are believed to be representative of what might similarly be found in pharma. This lighting is expected to be utilized in the inspection for defects of the NFISs addressed in this document. These levels might be different from levels specified in earlier publications of this document and other International Standards.

7 Test report

Each report of the testing performed in accordance with this document shall at least include the following information:

a) a reference to this document, i.e. ISO 21649:2023;

b) identification of the NFIS tested;

c) identification of the test system used;

d) identification of the test substance used;

e) the test results;

f) details of any deviation from this document;

g) specification of test system;

h) the name and address of the test facility;

i) the date of the test;

j) indication of re-use of NFISs for testing in accordance with 6.1.

8 Information supplied with the NFIS

8.1 General

The NFIS shall be accompanied by sufficient information to use it safely, taking into account the training and knowledge of the potential users, and to identify the manufacturer.

Instructions for use shall be included in the unit container.

The NFIS shall be accompanied by information, including instruction for use and markings on user packaging, that is sufficient for its safe use, considering the training and knowledge of intended

users and the intended use environment. The information required shall be determined through risk assessment and validated or justified as adequate for safe use using a usability engineering process (see 5.4).

Separately-delivered injector components shall identify the NFIS or the specific injector components with which they have been tested and demonstrated to be functionally compatible.

8.2 Marking

The NFIS and the unit container shall both be clearly marked with information that is sufficient for safe identification of the NFIS, unit container and contents, and for their safe storage. Any such marking shall be visible and legible. This shall be checked by visual inspection (normal or corrected-to-normal) at environmental lighting conditions of (215 ± 20) lx from a reading distance of 40 cm to 70 cm.

Guidance and particulars of marking for both the NFIS and the unit container are set out in Annex C.

8.3 Instructions for use

The NFIS and the unit container shall be accompanied by instructions for use that are sufficient for its safe use, taking into account the training and knowledge of potential users.

Guidance and particulars of what shall be covered by the instructions for use are set out in Annex C.

Annex A
(informative)

Two-sided tolerance limit factors (k)

Table A.1 shows the two-sided tolerance limit factors.

Gamma = confidence level (e.g. 95 %)

p = probability content level (as shown in columns below)

Table A.1 — Two-sided tolerance limit factors

Confidence = 95 %							
n	p = 0,750	p = 0,900	p = 0,950	p = 0,975	p = 0,990	p = 0,995	p = 0,999
2	22,383	31,092	36,519	41,308	46,944	50,813	58,844
3	5,937	8,306	9,789	11,101	12,647	13,710	15,920
4	3,818	5,368	6,341	7,203	8,221	8,921	10,377
5	3,041	4,291	5,077	5,774	6,598	7,165	8,345
6	2,638	3,733	4,422	5,034	5,758	6,256	7,294
7	2,391	3,390	4,020	4,579	5,241	5,697	6,647
8	2,223	3,156	3,746	4,269	4,889	5,316	6,206
9	2,101	2,986	3,546	4,044	4,633	5,039	5,885
10	2,008	2,856	3,393	3,871	4,437	4,827	5,640
11	1,934	2,754	3,273	3,735	4,282	4,659	5,446
12	1,874	2,670	3,175	3,624	4,156	4,522	5,287
13	1,825	2,601	3,093	3,531	4,051	4,409	5,156
14	1,783	2,542	3,024	3,453	3,962	4,312	5,044
15	1,747	2,492	2,965	3,386	3,885	4,230	4,949
16	1,716	2,449	2,913	3,328	3,819	4,158	4,865
17	1,689	2,410	2,868	3,277	3,761	4,095	4,792
18	1,665	2,376	2,828	3,231	3,709	4,039	4,727
19	1,643	2,346	2,793	3,191	3,663	3,988	4,669
20	1,624	2,319	2,760	3,154	3,621	3,943	4,616
21	1,607	2,294	2,731	3,121	3,583	3,903	4,569
22	1,591	2,272	2,705	3,091	3,549	3,865	4,526
23	1,576	2,251	2,681	3,063	3,518	3,831	4,486
24	1,563	2,232	2,658	3,038	3,489	3,800	4,450
25	1,551	2,215	2,638	3,015	3,462	3,771	4,415
26	1,539	2,199	2,619	2,993	3,437	3,744	4,385
27	1,529	2,184	2,601	2,973	3,415	3,720	4,356
28	1,519	2,170	2,585	2,954	3,393	3,696	4,330
29	1,510	2,157	2,569	2,937	3,373	3,675	4,304
30	1,501	2,145	2,555	2,921	3,355	3,654	4,281

Table A.1 *(continued)*

Confidence = 95 %							
n	*p* = 0,750	*p* = 0,900	*p* = 0,950	*p* = 0,975	*p* = 0,990	*p* = 0,995	*p* = 0,999
31	1,493	2,134	2,541	2,905	3,337	3,635	4,259
32	1,486	2,123	2,529	2,891	3,320	3,617	4,238
33	1,478	2,113	2,517	2,877	3,305	3,600	4,218
34	1,472	2,103	2,505	2,864	3,290	3,584	4,199
35	1,465	2,094	2,495	2,852	3,276	3,569	4,182
36	1,459	2,086	2,484	2,840	3,263	3,555	4,165
37	1,454	2,077	2,475	2,829	3,250	3,541	4,149
38	1,448	2,070	2,466	2,819	3,238	3,528	4,134
39	1,443	2,062	2,457	2,809	3,227	3,516	4,119
40	1,438	2,055	2,448	2,799	3,216	3,504	4,105
41	1,433	2,049	2,440	2,790	3,205	3,492	4,092
42	1,429	2,042	2,433	2,781	3,196	3,482	4,080
43	1,424	2,036	2,425	2,773	3,186	3,471	4,068
44	1,420	2,030	2,418	2,765	3,177	3,461	4,056
45	1,416	2,024	2,412	2,757	3,168	3,452	4,045
46	1,412	2,019	2,405	2,750	3,160	3,443	4,034
47	1,409	2,014	2,399	2,743	3,151	3,434	4,024
48	1,405	2,009	2,393	2,736	3,144	3,425	4,014
49	1,402	2,004	2,387	2,729	3,136	3,417	4,004
50	1,398	1,999	2,382	2,723	3,129	3,409	3,995
51	1,395	1,994	2,376	2,717	3,122	3,401	3,986
52	1,392	1,990	2,371	2,711	3,115	3,394	3,978
53	1,389	1,986	2,366	2,705	3,108	3,387	3,969
54	1,386	1,982	2,361	2,700	3,102	3,380	3,961
55	1,383	1,978	2,356	2,694	3,096	3,373	3,953
56	1,381	1,974	2,352	2,689	3,090	3,367	3,946
57	1,378	1,970	2,347	2,684	3,084	3,361	3,939
58	1,376	1,967	2,343	2,679	3,079	3,355	3,932
59	1,373	1,963	2,339	2,675	3,073	3,349	3,925
60	1,371	1,960	2,335	2,670	3,068	3,343	3,918
61	1,369	1,957	2,331	2,666	3,063	3,338	3,912
62	1,366	1,953	2,327	2,661	3,058	3,332	3,905
63	1,364	1,950	2,324	2,657	3,053	3,327	3,899
64	1,362	1,947	2,320	2,653	3,048	3,322	3,893
65	1,360	1,944	2,317	2,649	3,044	3,317	3,887
66	1,358	1,941	2,313	2,645	3,039	3,312	3,882
67	1,356	1,939	2,310	2,641	3,035	3,307	3,876
68	1,354	1,936	2,307	2,638	3,031	3,303	3,871
69	1,352	1,933	2,304	2,634	3,027	3,298	3,866

Table A.1 *(continued)*

Confidence = 95 %							
n	*p* = 0,750	*p* = 0,900	*p* = 0,950	*p* = 0,975	*p* = 0,990	*p* = 0,995	*p* = 0,999
70	1,350	1,931	2,300	2,631	3,023	3,294	3,861
71	1,349	1,928	2,297	2,627	3,019	3,290	3,856
72	1,347	1,926	2,295	2,624	3,015	3,285	3,851
73	1,345	1,923	2,292	2,621	3,011	3,281	3,846
74	1,344	1,921	2,289	2,617	3,008	3,277	3,841
75	1,342	1,919	2,286	2,614	3,004	3,274	3,837
76	1,341	1,917	2,284	2,611	3,001	3,270	3,832
77	1,339	1,914	2,281	2,608	2,997	3,266	3,828
78	1,337	1,912	2,278	2,605	2,994	3,262	3,824
79	1,336	1,910	2,276	2,603	2,991	3,259	3,820
80	1,335	1,908	2,274	2,600	2,988	3,255	3,816
81	1,333	1,906	2,271	2,597	2,984	3,252	3,812
82	1,332	1,904	2,269	2,594	2,981	3,249	3,808
83	1,330	1,902	2,267	2,592	2,978	3,246	3,804
84	1,329	1,900	2,264	2,589	2,975	3,242	3,800
85	1,328	1,899	2,262	2,587	2,973	3,239	3,797
86	1,327	1,897	2,260	2,584	2,970	3,236	3,793
87	1,325	1,895	2,258	2,582	2,967	3,233	3,790
88	1,324	1,893	2,256	2,580	2,964	3,230	3,786
89	1,323	1,892	2,254	2,577	2,962	3,227	3,783
90	1,322	1,890	2,252	2,575	2,959	3,225	3,780
91	1,321	1,888	2,250	2,573	2,957	3,222	3,776
92	1,320	1,887	2,248	2,571	2,954	3,219	3,773
93	1,318	1,885	2,246	2,569	2,952	3,216	3,770
94	1,317	1,884	2,244	2,566	2,949	3,214	3,767
95	1,316	1,882	2,242	2,564	2,947	3,211	3,764
96	1,315	1,881	2,241	2,562	2,944	3,209	3,761
97	1,314	1,879	2,239	2,560	2,942	3,206	3,758
98	1,313	1,878	2,237	2,558	2,940	3,204	3,755
99	1,312	1,876	2,236	2,556	2,938	3,201	3,752
100	1,311	1,875	2,234	2,555	2,936	3,199	3,750
102	1,309	1,872	2,231	2,551	2,931	3,194	3,744
104	1,308	1,869	2,228	2,547	2,927	3,190	3,739
106	1,306	1,867	2,225	2,544	2,923	3,186	3,734
108	1,304	1,864	2,222	2,541	2,919	3,181	3,729
110	1,302	1,862	2,219	2,537	2,916	3,177	3,724
112	1,301	1,860	2,216	2,534	2,912	3,173	3,720
114	1,299	1,858	2,213	2,531	2,909	3,170	3,715
116	1,298	1,855	2,211	2,528	2,905	3,166	3,711
118	1,296	1,853	2,208	2,525	2,902	3,162	3,707