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

Part 1: Needle-based injection systems

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

Partie 1: Systèmes d'injection à aiguille

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Contents

Page

Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

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 11608-1 was prepared by Technical Committee ISO/TC 84, *Devices for administration of medicinal products and intravascular catheters*.

This second edition cancels and replaces the first edition (ISO 11608-1:2000), which has been technically revised.

ISO 11608 consists of the following parts, under the general title *Needle-based injection systems for medical use — Requirements and test methods*:

— *Part 1: Needle-based injection systems*

— *Part 2: Needles*

— *Part 3: Finished containers*

— *Part 4: Requirements and test methods for electronic and electromechanical pen-injectors*

— *Part 5: Automated functions*

Introduction

This part of ISO 11608 covers needle-based injection systems (referred to as NISs) primarily intended for human use. It provides performance requirements regarding essential aspects so that variations of design are not unnecessarily restricted.

This part of ISO 11608 should be used in conjunction with the other parts of ISO 11608.

The first edition of this part of ISO 11608 introduced the concept of interchangeability and the labelling designations “Type A” (i.e. interchangeable) and “non-Type A” for needles and container systems. Since its promulgation, experience has shown that the complexity of these systems makes it very difficult to ensure functional compatibility as defined in the different parts of this International Standard, particularly when products are made by different manufacturers. Based on this experience, it is believed that the Type A designation does not represent adequate guidance to the user in making decisions on the compatibility of needles and containers with specific needle-based injector systems. As such, the labelling designation “Type A” has been removed. The design requirements related to system function have been maintained as a guide to assist manufacturers during the design phase, supporting the achievement of cross-platform compatibility. However, these design requirements are an insufficient replacement for system testing of the components and, where possible, direct communication and/or quality agreements between system component manufacturers. Therefore, given the patient convenience benefits associated with cross-platform compatibility, manufacturers of needles, containers and needle-based injectors shall label their products with the specific system components that have been tested and demonstrated to be functionally compatible.

The sampling plans for inspection selected for this part of ISO 11608 are intended to verify the design at a high confidence level. The sampling plans for inspection do not replace the more general manufacturing quality systems that appear in standards on quality systems, for example the ISO 9000 series and ISO 13485.

Materials to be used for construction are not specified, as their selection will depend on the design, the intended use and the process of manufacture used by individual manufacturers.

There are other international and national standards and guidance publications and, in some countries, national regulations that are applicable to medical devices and pharmaceuticals. Their requirements might supersede or complement this part of ISO 11608. Developers and manufacturers of NISs are encouraged to investigate and determine whether there are any other requirements relevant to the safety or marketability of their products.

Manufacturers are expected to follow a risk-based approach during the design, development and manufacture of the product. Given the specific medicinal product and intended use, this might result in product-specific requirements and test methods that differ from what is outlined in this part of ISO 11608.

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

Part 1: Needle-based injection systems

1 Scope

This part of ISO 11608 specifies requirements and test methods for needle-based injection systems (NISs) intended to be used with needles and with replaceable or non-replaceable containers. Containers covered in this part of ISO 11608 include single- and multi-dose syringe-based and cartridge-based systems, filled either by the manufacturer or by the end-user.

Additional guidance for NISs equipped with electronic or electromechanical components and NISs equipped with automated functions is given in ISO 11608-4 and ISO 11608-5 respectively.

Needle-free injectors, and requirements relating to methods or equipment associated with end-user filling of containers, are outside the scope of this part of ISO 11608.

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 10993-1, *Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process*

ISO 11608 (all parts), *Needle-based injection systems for medical use — Requirements and test methods*

ISO 13485:2003, *Medical devices — Quality management systems — Requirements for regulatory purposes*

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

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

ISO/IEC Guide 98-3, *Uncertainty of measurement — Part 3: Guide to the expression of uncertainty in measurement (GUM:1995)*

IEC 60068-2-6:2007, *Environmental testing — Part 2-6: Tests — Test Fc: Vibration (sinusoidal)*

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

IEC 60601-1-2:2007, *Medical electrical equipment — Part 1-2: General requirements for basic safety and essential performance — Collateral standard: Electromagnetic compatibility — Requirements and tests*

IEC 62366, *Medical devices — Application of usability engineering to medical devices*

3 Terms and definitions

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

3.1
cap
part of the NIS intended to protect the injector and its contents

3.2
container
primary packaging that contains the medicinal product for injection (either single-compartment or multi-compartment)

3.3
dose delivery efficiency
ratio of expelled dose to fill volume

NOTE 1 Dose delivery efficiency is expressed as a percentage.

NOTE 2 Delivery efficiency can be used to evaluate dose accuracy for NISs designed to fully empty single-dose containers filled by the user.

3.4
dialling resolution
smallest possible increment to be selected between dose amounts

3.5
dose accuracy
accuracy with which the NIS delivers a pre-set dose of medicinal product

3.6
"dose delivered" indication
dose number shown in the dose window indicating the amount of medicinal product delivered

NOTE 1 This applies to variable multi-dose NISs that allow the setting of a dose greater than the remaining volume.

NOTE 2 If the dose window indicates the amount of medicinal product yet to be delivered, then the "dose delivered" indication can be determined as the intended dose minus the indication of medicinal product yet to be delivered.

3.7
manufacturer-filled
container supplied to the user pre-filled by the manufacturer of medicinal products

NOTE This medicinal product can be in liquid form or lyophilized with diluent in the same container.

3.8
minimum deliverable dose
minimum dose that is ensured by the manufacturer to be delivered in a single-dose manufacturer-filled NIS designed to fully empty the container

3.9
NIS
needle-based injection system
injection system intended for parenteral administration by injection of medicinal products using a needle and a multi-dose or single-dose container

NOTE This term may also be referred to as "system" or "injector" in this part of ISO 11608.

3.10
pre-setting
procedure by which individual amounts of medicinal product can be selected for injection by the user

NOTE The doses may be pre-set by the manufacturer or the user.

3.11
residual scale
graduated scale which indicates the remainder of medicinal product in the container

3.12
user packaging
what is provided to the user with one or a collection of devices of the same item and from the same manufacturing batch, including the directions for use

3.13
user-filled
container that is filled or reconstituted (if in lyophilized form) by the user from a separate medicinal product or diluent container

4 Symbols and abbreviated terms

NIS Needle-based injection system.

V_{set} One of the three pre-set doses (expressed as a volume, in millilitres) used in determining the dose accuracy for a given NIS. 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 1 Recommended doses as specified in the instructions for use may differ from the pre-set doses used for determining the dose accuracy.

NOTE 2 System designations B1 and D1 define V_{set} to be equal to the manufacturer-filled or user-filled volumes. System designations B2 and D2 define V_{set} to be equal to a single pre-set dose representing a portion of the manufacturer-filled or user-filled volumes. In the case of last-dose accuracy assessments for system designations A and C, V_{set} is equal to V_{mid}, the TP, or dose error (evaluated over a range of doses within a specified percentage of the TP).

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 Density, expressed in grams per millilitre.

p Probability content.

Y Number of pens required for a given test.

R Number of replicates required for a given test. A replicate is a random sequence of V_{min}, V_{mid}, and V_{max}. There are six possible replicates.

n Number of measurements, V_{meas}, to be made for each V_{set}.

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

$$\bar{x} = \sum V_{meas} / n .$$

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

$$s = \left[\sum (V_{meas} - \bar{x})^2 / (n-1) \right]^{1/2} .$$

k — k value, or tolerance limit factor, determined from the confidence level (95 %), probability content, p, and number of accuracy measurements, n, conducted at each dose setting.

k_{act} — Actual k value, determined from the following equations:

Two-sided

$$\text{Min}\left[\frac{(U-\bar{x})}{s},\frac{(\bar{x}-L)}{s}\right]$$

One-sided

$$\left[\frac{(\bar{x}-L)}{s}\right] \text{ or } \left[\frac{(U-\bar{x})}{s}\right]$$

k_{tar} — Target k value, found from the look-up table in ISO 16269-6:2005 (Annexes D and E), or Annex B.

DR — Dialling resolution, the minimum dialling increment of the NIS.

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.

TP — The transition point volume, in millilitres, at which the upper and lower specification limits for V_{set} change from absolute terms to relative terms (i.e. V_{set} where α and β are equal):

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

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

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

RF — Radio frequency

5 Requirements

5.1 General

Companies wishing to verify a NIS shall ensure that the system meets the requirements of this part of ISO 11608. In addition, companies shall ensure that the appropriate components (e.g. needles and containers) and features (e.g. electromechanical drive systems and automated functions) specified for use in the system satisfy the relevant parts of ISO 11608.

5.2 System designations

Given the differences in device designs and containers (e.g. multi-dose, single dose with partial evacuation, and single-dose with full evacuation), the following system designations are provided to clearly associate the appropriate test and dose accuracy method with the injection system under consideration. Containers can be either manufacturer-filled or user-filled.

Table 1 shows the various needle-based injector system designations.

Table 1 — System designations

Multi-dose container	Single-dose container
A Needle-based injection device with replaceable container. Each container holds multiple doses, the size of which may be fixed or variable (pre-set by the user).	B1 Needle-based injection device with replaceable container. Each container holds a single dose, whereby the entire deliverable volume is expelled.
	B2 Needle-based injection device with replaceable container. Each container holds a single dose, whereby a portion of the deliverable volume is expelled.
C Needle-based injection device with integrated non-replaceable container. Each container holds multiple doses, the size of which may be fixed or variable (pre-set by the user).	D1 Needle-based injection device with integrated non-replaceable container. Each container holds a single dose, whereby the entire deliverable volume is expelled.
	D2 Needle-based injection device with integrated non-replaceable container. Each container holds a single dose, whereby a portion of the deliverable volume is expelled.

5.3 Risk analysis requirements

The manufacturer shall conduct risk assessments in accordance with ISO 14971. These risk assessments shall consider all aspects of the development, manufacture and intended use of the NIS for medical use. The NIS shall conform to the usability requirements specified in IEC 62366.

5.4 Uncertainty of measurement and conformance with specifications

Measurement uncertainty shall be evaluated and expressed by the laboratory performing the test in accordance with ISO/IEC Guide 98-3 (GUM).

Conformance with specifications is established in accordance with ISO 14253-1.

5.5 General design requirements

a) The container holder shall allow visibility of the deliverable volume. The manufacturer shall determine, by risk analysis, if a residual scale is required and how much of the deliverable volume shall be visible.

b) With the exception of system designations B2 and D2, NISs shall be designed in such a way that they are able to accurately deliver the entire labelled volume from the container for which they are designed.

c) NISs with system designation B1 where the container is user-filled shall be designed in such a way that they are capable of delivering the maximum volume needed to fill the container, as specified in the labelling.

d) When the injection system requires the user to pre-set the dose, the injector 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 setting specified by the physician (e.g. number, letter, percentage) as appropriate for the drug to be delivered. When the dose has been pre-set by the manufacturer, the dose can be indicated by the device or the system labelling, as appropriate.

e) There shall be an indication of the pre-setting by visual and either tactile and/or audible means.

f) The NIS shall indicate, at least by visual means, that it is ready for injection.

g) The state of the NIS, when ready to deliver a dose, shall be different from its state when the dose has been delivered. The difference shall be visible.

h) The NIS shall indicate, by visual, audible or tactile means, or any combination of these, that the injection stroke has been completed.

i) NISs with system designation D2 shall be designed in such a way that it is impossible to deliver the remaining volume following the actuation and that it is impossible to reactivate the device.

j) Variable multi-dose NISs (system designations A and C) shall be designed so that they:

   1) do not allow a larger dose to be pre-set than is left in the container, or

   2) do not allow dose delivery if the pre-set amount exceeds the amount of medicinal product left in the container, or

   3) indicate the amount of medicinal product delivered, or

   4) indicate the amount of medicinal product not delivered (of the pre-set dose).

k) Fixed multi-dose NISs shall not allow pre-setting of the dose if a volume that is insufficient for the full fixed dose remains.

l) The NIS shall be designed to function with its specified needles. ISO 11608-2 provides guidance for needles.

m) The NIS shall be designed to function with its specified containers. ISO 11608-3 provides guidance for containers.

n) If the NIS is an electromechanically driven injector, the requirements of ISO 11608-4 and ISO 11608-5 shall be fulfilled.

o) If the NIS contains electronic or electromechanical components and/or software, the requirements of ISO 11608-4 shall be fulfilled.

p) To avoid inadvertent disabling of the NIS containing replaceable batteries, it shall not be possible to remove the batteries unless two independent movements are applied.

q) If designed with small parts that might be swallowed, the NIS labelling shall include warnings preventing access by children under the age of 3 years.

r) If the NIS contains batteries, it shall be designed to allow the user to determine the state of the power supply.

s) If the NIS contains software, the software shall be designed based on a life-cycle model in accordance with IEC 62304. The NIS shall fulfil the applicable requirements of IEC 62304 including connection to other equipment.

t) The risk analysis shall take into consideration the use of alarms, as appropriate, as described in IEC 60601-1-11.

u) Adverse effects of the medicinal product contact with the NIS shall be assessed and mitigated through risk assessment.

v) Biological requirements of the NIS shall be established in accordance with ISO 10993-1.

NOTE It is preferable that the design process incorporate environmentally conscious design (see IEC 60601-1-9).

w) Where requirements in this part of ISO 11608 provide a test method without acceptance criteria, the manufacturer shall establish a specification and acceptance criteria appropriate for the intended use of the device, using a risk-based approach (consistent with ISO 14971 and IEC 62366).

6 Reagent and apparatus

6.1 General

Any suitable test system can be used, 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 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).

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 Gauge R&R/tolerance range 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.

All doses, V_{set}, delivered are recorded gravimetrically, G_{meas}, (expressed in grams). These recordings are converted to volumes, V_{meas}, by using the density, ρ, (expressed in grams per millilitre) for the test liquid at environmental conditions. The following equation can be used to convert gravimetric measurements to volumetric:

$$V_{meas} = G_{meas}/\rho \quad (1)$$

6.2 Test liquid

The test liquid is the original medicinal product intended to be injected by the NIS, or a liquid with similar physical properties.

6.3 Balance

The balance shall have a resolution of 1 % of the minimum dose delivery.

6.4 Test surface for free-fall testing

The test surface shall be made of smooth, hard, rigid steel of 3 mm thickness, backed by wood whose thickness is greater than 10 mm.

7 Determination of dose accuracy

7.1 General

Determination of dose accuracy is a required element that shall be met by the NIS, as defined by the design specifications. Where regulatory requirements are more stringent, or where the risk assessment dictates, the dose accuracy acceptance criteria shall be adjusted to ensure the system meets them. If these regulatory requirements are less stringent, then the manufacturer can include them in the risk assessment as justification for widening the acceptance criteria.

Dose accuracy is determined by selecting and testing a variable number of NISs. The number depends on the container and accuracy requirements for a given test. In the specific instance of user-filled single-dose needle-based systems designed to fully empty the container, accuracy can be evaluated as dose-delivery efficiency. In the instance of manufacturer-filled single-dose NISs designed to fully empty the container, accuracy can be evaluated as the minimum deliverable dose (i.e. the labelled volume).

Assuming that the accuracy measurements are normally distributed (or can be transformed to normal) and that each measurement is independent, the following methods enable accuracy measurements to be used as the basis for determining a statistical tolerance interval for each V_{set}, i.e. an interval where there is a fixed probability (confidence level) that the interval will contain at least a proportion (probability content, p) of the true population from which the sample is taken. The statistical tolerance interval is two-sided or one-sided (e.g. dose efficiency and minimum-deliverable-dose assessments) and the limits of the interval are called “statistical tolerance limits” or “natural limits of the process”.

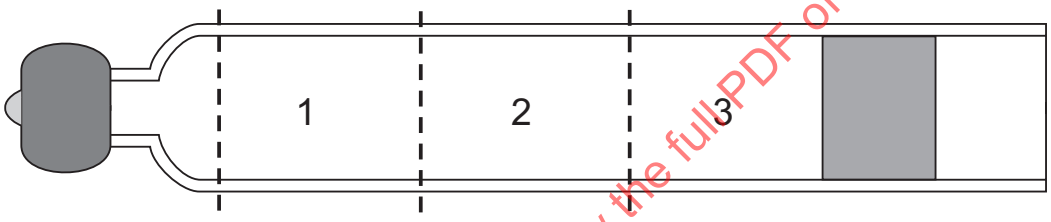
Table 2 provides a summary, by system designation, of the subclauses that are required in order to complete an assessment of dose accuracy.

Table 2 — Dose accuracy assessment matrix

Dose accuracy matrix	System designation					
	A	B1	B2	C	D1	D2
Determine doses needed	7.3.1	7.3.2	7.3.2	7.3.1	7.3.2	7.3.2
Determine accuracy limits	7.4.2.1	7.4.2.2	7.4.2.1	7.4.2.1	7.4.2.2	7.4.2.1
Determine last-dose accuracy limits (variable dose only)	7.4.3	N/A	N/A	7.4.3	N/A	N/A
Calculate last-dose error (variable dose only)	10.3	N/A	N/A	10.3	N/A	N/A
Calculate dose efficiency (user-filled only)	N/A	7.4.4	N/A	N/A	7.4.4	N/A
Calculate tolerance intervals	7.4.5	7.4.5	7.4.5	7.4.5	7.4.5	7.4.5

7.2 Dosing regions

For multi-dose containers, the dosing regions are as defined in Figure 1.



Key

1 front 1/3
2 middle 1/3
3 rear 1/3

Figure 1 — Schematic showing three divisions

NOTE 1 If the maximum dose setting is greater than one third of the labelled volume, the container can be divided into two sections as opposed to three.

NOTE 2 The illustrated container design is an example. Different container designs require verification that all three regions (full, half-way used and almost empty) perform predictably.

7.3 Dose settings

7.3.1 Multi-dose containers (system designations A and C)

7.3.1.1 Variable dose devices

a) Three dose sizes are used; V_{set} is equal to one of minimum (V_{min}), midpoint (V_{mid}) and maximum (V_{max}).

b) One dose of each V_{set} is taken from each container.

c) All replicate sequences are tested (V_{min}, V_{mid}, V_{max}; V_{max}, V_{min}, V_{mid}; etc.). Full details are given in Annex A.

d) Dosing is designed such that V_{set} is delivered from the front 1/3, middle 1/3 and rear 1/3 divisions of the container closure, as shown in Figure 1, or is uniformly sampled from regions representing the deliverable volume of the container, as determined in the risk assessment.

7.3.1.2 Fixed-dose devices

a) One dose size is used; V_{set} is equal to the fixed dose.

b) One dose is taken from each container.

c) Dosing is designed such that V_{set} is delivered from the front 1/3, middle 1/3 and rear 1/3 divisions of the container closure, as shown in Figure 1, or is uniformly sampled from regions representing the deliverable volume of the container, as determined in the risk assessment.

7.3.2 Single-dose containers (system designations B and D)

7.3.2.1 Complete evacuation

For system designations B1 and D1, one dose is used; V_{set} is equal to the delivered dose.

7.3.2.2 Partial evacuation

7.3.2.2.1 Variable dose devices

Three dose sizes are used; V_{set} is equal to minimum (V_{min}), midpoint (V_{mid}) and maximum (V_{max}).

7.3.2.2.2 Fixed dose devices

One dose size is used; V_{set} is equal to the pre-set dose.

7.4 Assessment

7.4.1 General

To pass the dose accuracy requirement, there shall be a 95 % confidence that at least the probability content, p, of all doses delivered will fall within the proposed upper and lower specification limits for the three dose settings (one dose setting in the case of fixed-dose systems).

To pass the minimum deliverable dose requirement (for system designations B1 and D1 with manufacturer-filled containers), there shall be a 95 % confidence that at least the probability content, p, of all doses delivered are above the lower specification limit, which is defined by the minimum deliverable dose specified by the drug labelling.

To pass the dose delivery efficiency requirement (for system designations B1 and D1 with user-filled containers), there shall be a 95 % confidence that at least the probability content, p, of all delivery efficiencies are above the lower specification limit for dose efficiency as determined from the risk assessment. Calculate dose delivery efficiency in accordance with 7.4.4.

To pass the last-dose accuracy requirement (for system designations A and C), where the device allows setting a dose greater than the remaining volume, there shall be a 95 % confidence that at least the probability content, p, of all dose error calculations will fall within the proposed upper and lower specification limits for allowable dose error.

Only one dose per injector can be used for each V_{set} for a given test.

Probability content, p, is defined by a specific test and is shown in Table 3.

7.4.2 Determination of dose accuracy limits

7.4.2.1 Two-sided dose accuracy limits (system designations A, C, B2, D2)

Rule 1: Absolute error, α, expressed in millilitres, is equal to the minimum dialling resolution, DR, of the device and is used when V_{set} is equal to or below the TP.

Rule 2: Relative error, β, expressed as a percentage, is equal to 5 % of V_{set} and is used when V_{set} is above the TP.

TP is equal to V_{set} where α and β are equal:

$$TP = \frac{100 \times \alpha}{\beta}$$

Rule 3: For fixed-dose devices, the absolute error, α, is 0,01 ml if the fixed dose is below 0,2 ml and 5 % if the fixed dose is above 0,2 ml.

EXAMPLE 1 For DR equal to 0,01 ml, α is 0,01 ml, β is 5 % and, therefore:

$$TP = \frac{100 \times 0{,}01}{5} = 0{,}20$$

EXAMPLE 2 For DR equal to 0,005 ml, α is 0,005 ml, β is 5 % and, therefore:

$$TP = \frac{100 \times 0{,}005}{5} = 0{,}10$$

EXAMPLE 3 The upper and lower specification limits are calculated as follows:

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

$$U = V_{set} + \alpha;$$

$$L = V_{set} - \alpha.$$

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

$$U = V_{set} + (\beta \cdot V_{set})/100;$$

$$L = V_{set} - (\beta \cdot V_{set})/100.$$

For system designations A, C, B2 and D2, if, according to the manufacturer's risk assessment, the intended dose sizes and accuracy requirements are more appropriately specified individually (i.e. rules 1, 2 and 3 are not applied) rather than by absolute or relative ranges, the dose sizes tested and their specification limits shall be specified in the labelling. In such a case, the specification limits can be no greater than the DR of the needle-based system. For system designation D2, the dosing resolution requirement does not apply.

For system designations A and C, if, according to the manufacturer's risk assessment, a specific dose is to be treated differently from all other doses (e.g. first dose when the intended use of the system does not require priming), then (after performing dose accuracy as described above) give special consideration when analysing those specific data points:

a) each data point from the specific doses of a container shall satisfy the dose accuracy requirement based on specification limits determined from the risk assessment;

b) all of those specific dose data points may be excluded from the statistical analysis of all other doses.

7.4.2.2 One-sided dose accuracy limits (system designations B1 and D1)

a) For user-filled containers, the one-sided lower specification limit for dose delivery efficiency assessments is determined from the risk assessment.

b) For manufacturer-filled containers, the one-sided lower specification limit for the minimum deliverable dose is determined from the drug labelling.

7.4.3 Determination of last-dose error and last-dose accuracy limits (system designations A and C)

For variable-dose devices that do not allow the setting of a dose greater than the remaining volume, establish dose accuracy limits as described in 7.4.2 using either V_{set} equal to V_{min} or the TP dose (the manufacturer shall determine which to use based on the risk assessment).

For variable-dose devices that do allow the setting of a dose greater than the remaining volume, the last dose is evaluated in terms of dose error due to the fact that normal variation in system dimensions makes it impossible to set the exact same last dose from one device or container to the next. To address the uncertainty of the exact last dose to be evaluated, a number of different last doses are evaluated as long as they fall within 10 % of the TP, so that a mean dose error (ideally centred on zero) is calculated for each of the doses. Individual last-dose errors (expressed as a percentage) are calculated as shown in the following example using a TP of 0,20 ml:

a) The range of doses that can be used to determine last-dose accuracy would be from 0,18 ml to 0,22 ml for this example, where the TP is 0,20 ml. This range is ±10 % of the TP. Any doses for which the NIS displays a value above or below this range would not be acceptable for use in determining the last-dose accuracy.

b) For each last-dose measurement, V_{meas}, calculate the last-dose error, as a percentage, as:

$$\frac{V_{meas} - \text{dose delivered indication}}{\text{dose delivered indication}} \times 100$$

c) The upper specification limit, U, for the mean last dose error above the TP (i.e. relative error):

$U = 5\ \%$

d) The lower specification limit, L, for the mean last-dose error below the TP (i.e. absolute error based on the DR and expressed as a negative percentage):

1) $$\frac{\text{DR}}{\text{low end of the last-dose range}}$$

In this example, DR is 0,01 ml; the low end of the last-dose range is 0,18 ml.

2) $$L = \frac{0,01}{0,18} \times 100 = -5,6$$

NOTE If, according to the manufacturer's risk assessment, a different last-dose measurement range is used (e.g. 20 % around the TP), the specification limits for last-dose error shall be stated in the instructions for use.

7.4.4 Calculation of dose delivery efficiency (system designations B1 and D1, user-filled)

a) Measure the mass of the container as received by the user (i.e. empty) as m_1;

b) Measure the mass of the filled container as m_2;

c) Measure the mass of the container and any residue after delivery as m_3;

d) Calculate dose efficiency by:

$$\frac{m_2 - m_3}{m_2 - m_1} \times 100$$

NOTE For system designation D1, the container is defined as the entire device (i.e. a device with an empty integrated non-replaceable container) prior to user-filling.

7.4.5 Calculation of tolerance intervals

For a given test's dose accuracy measurements:

a) determine the mean, $\bar{x}$, and standard deviation(s);

b) determine the actual k value, or tolerance limit factor;

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

$$\bar{x} \pm k \cdot s \tag{2}$$

For system designations B1 and D1, the one-sided statistical tolerance interval is calculated using the mean, $\bar{x}$, minus or plus the standard deviation(s), multiplied by a tolerance limit factor, k:

$$\bar{x} - k \cdot s \quad \text{or} \quad \bar{x} + k \cdot s \tag{3}$$

where

$\bar{x}$ is the mean of the sample;

k is the tolerance limit factor;

s is the standard deviation of the sample.

The tolerance limit factor is determined based upon the confidence level (95 %), probability content, p, and the number of measurements, n, taken.

NOTE 1 As an example, for dose efficiency, the one-sided evaluation would require a 95 % probability that at least 97,5 % of all doses have a dose efficiency greater than or equal to x % (the value of x to be determined by the risk assessment).

NOTE 2 ISO 16269-6:2005, Annex E, 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 provides an example of an accuracy assessment. Table B.1 provides one-sided tolerance limits for the 95 % confidence level for both the 0,95 and 0,975 probability contents, p, and Table B.2 contains more comprehensive two-sided tolerance limits for the 95 % confidence level.

8 Preparation and operation of NISs

Prepare the NIS in accordance with the instructions for use.

Carry out the test so that the operation of the NIS simulates the operations described in the instructions for use.

Operate the NIS manually or automatically.

Determine the dose delivered, G_{meas}, by reading the balance right after completion of the injection stroke or as specified in the instructions for use.

When the maximum number of operations has been reached for a NIS with a replaceable container and with a built-in limited number of operations, replace the NIS with a new one.

9 Test matrix

Table 3 summarizes test requirements for the system designations described in 5.1. Clause A.3 provides the rationale for the required tests.

a) For each V_{set}, the target k corresponds to the number of measurements per V_{set}, n. If the total number of measurements is changed, the corresponding target k shall be changed as well.

b) Target k values for two-sided tolerance intervals are selected from ISO 16269-6 or Table B.2.

c) Target k values for one-sided tolerance intervals are selected from ISO 16269-6 or Table B.1.

Table 3 — Test matrix

System designation									
A	B	C	D	Brief description	Probability content p	Replicates per injector R	Total measurements per V_{set} n	Two-sided target k	One-sided target k
Cool, standard, warm atmosphere (10.2)	Cool, standard, warm atmosphere (10.2)	Cool, standard, warm atmosphere (10.2)	Cool, standard, warm atmosphere (10.2)	Dose accuracy (DA) testing at 5 °C, 23 °C and 40 °C	0,975	1	60	2,670	2,384
Last-dose accuracy (10.3)	Not applicable	Last-dose accuracy (10.3)	Not applicable	DA at the last-dose indication	0,975	One last dose only	60	2,670	2,384
Life-cycle test (10.4)	Life-cycle test (10.4)	Not applicable	Not applicable	Cycle 1,5 × expected life, then standard DA	0,95	1	20	2,760	2,396
Free-fall [10.5 a) and c), system designation A, B1, B2]	Free-fall [10.5 a) and c), system designation A, B1, B2)	Not applicable	Not applicable	1 m drop × 3 orientations, then inspection and standard DA	0,95	1	20	2,760	2,396
Not applicable	Not applicable	Free-fall ([10.5 b) and d), system designation C, D1, D2]	Free-fall [10.5 b) and d), system designation C, D1, D2]	1 m drop × 3 orientations, then inspection and standard DA	0,95	1	21	2,731	2,371
Dry heat/cold storage (10.6)	Dry heat/cold storage (10.6)	Dry heat/cold storage (10.6)	Dry heat/cold storage (10.6)	Condition at 70 °C or −40 °C, then standard DA	0,975	1	60	2,670	2,384
Damp heat (10.7)	Damp heat (10.7)	Not applicable	Not applicable	Condition at 40 °C and 93 % RH, then standard DA	0,95	1	20	2,760	TBD
Cyclical (10.8)	Cyclical (10.8)	Not applicable	Not applicable	Cycle between 5 °C and 55 °C × 6 over 6 days, then standard DA	0,95	1	20	2,760	2,396

Table 3 (*continued*)

System designation									
A	B	C	D	Brief description	Probability content p	Replicates per injector R	Total measurements per V_{set} n	Two-sided target k	One-sided target k
Vibration (10.9)	Vibration (10.9)	Vibration (10.9)	Vibration (10.9)	Vibration, then inspection and standard DA	0,95	1	20	2,760	2,396
Additional requirements for a device with electronics									
Electrostatic (10.10.2)	Electrostatic (10.10.2)	Electrostatic (10.10.2)	Electrostatic (10.10.2)	Electrostatic discharge, then inspection and standard DA	0,95	1	20	2,760	2,396
RF fields (10.10.3)	RF fields (10.10.3)	RF fields (10.10.3)	RF fields (10.10.3)	RF interference, then inspection and standard DA	0,95	1	20	2,760	2,396

10 Test descriptions

10.1 General

For each test described in Clause 10, perform the following evaluations after each pre-conditioning and testing requirement.

a) Perform a visual inspection in accordance with 11.1.

b) Perform a container inspection in accordance with 11.2.

c) Conduct dose accuracy testing and evaluate dose accuracy acceptance criteria in accordance with 11.3.

d) Except for pre-conditioning as described in 10.3 and 10.4, perform full functional testing based on the instructions for use.

e) Unless otherwise instructed for a given test description, the following environmental conditions apply (the assembled NIS with the container and unattached needle is allowed to acclimatize for at least 4 h):

— temperature: (23 ± 5) °C;

— relative humidity: (50 ± 25) %RH.

For system designations A and C, prepare injections in such a way that 1/3 are dosed from the front, 1/3 are dosed from the middle and 1/3 are dosed from the rear of the container (see Figure 1). All replicate sequences should be delivered from each section of the container, but this is not a requirement unless specified.

NOTE 1 For 10.2, 10.3, 10.4, 10.6 and 10.7, container inspection is not required.

NOTE 2 For free-fall testing, container inspection is not necessary as the evaluation has already been conducted as described in 10.5.

10.2 Cool, standard and warm atmosphere testing

10.2.1 Pre-conditioning

The assembled NIS with the container and unattached needle is placed in a test chamber for at least 4 h in the atmospheres given in Table 4.

Table 4 — Test conditions

Condition	Cool	Standard	Warm
Temperature °C	(5 ± 3)	(23 ± 5)	(40 ± 2)
Humidity %RH	No humidity requirement	(50 ± 25)	(50 ± 10)

10.2.2 Testing

For system designations A and B, conduct an accuracy measurement of the same set of systems at each of the conditions specified in Table 4. For system designations C and D, conduct an accuracy measurement of three different sets of systems at each of the conditions specified in Table 4.

For multi-dose systems (system designations A and C), prepare injectors in such a way that 1/3 are dosed from the front, 1/3 are dosed from the middle and 1/3 are dosed from the rear of the container (see Figure 1). All replicate sequences should be delivered from each section of the container, but this is not a requirement unless specified.

10.3 Last-dose testing (system designations A and C only)

10.3.1 General

Fixed-dose devices are excluded from this requirement [general design requirements are given in 5.5 j)]. Here, last-dose accuracy is part of the general dose accuracy requirement, which shall include a representative sample of these last doses.

10.3.2 Pre-conditioning

Select the same injectors previously used for determining dose accuracy in accordance with 10.2 (for system designation C, use new injectors).

For variable-dose devices that do not allow the setting of a dose greater than the remaining volume, operate each device until a dose, V_{set}, equal to either the V_{min} or transition point, TP, dose remains (the manufacturer shall determine which to use, based on the risk assessment).

For variable-dose devices that do allow the setting of a dose greater than the remaining volume, operate each device until the remaining deliverable volume is within 10 % of the TP.

10.3.3 Testing

For variable-dose devices that do not allow the setting of a dose greater than the remaining volume, use a V_{set} equal to the TP or V_{min}.

For variable-dose devices that do allow the setting of a dose greater than the remaining volume, use a V_{set} equal to V_{max}, or any dose sufficiently high to ensure that the plunger drive mechanism travel limit is engaged within 10 % of the TP.

10.4 Life-cycle testing (systems designations A and B only) — Pre-conditioning

The same systems as used in 10.2 shall be used (with new containers). This test is only required for system designations A and B.

Select and simulate operation of each feature of the injector (cap and needle removal and attachment, injection, etc.). The injectors shall be operated 1,5 times the maximum number of actuations expected during its lifetime. The test protocol shall take into consideration the intended use as described in the instructions for use.

If the system is designed to stop working after a limited time or number of operations, this total number of operations shall be adopted for this test.

10.5 Free-fall testing

The following list describes free-fall testing of cylindrical devices in both vertical and horizontal orientations. If, as per the risk assessment, different orientations are determined to be “worst-case”, those orientations shall be used.

NOTE For non-cylindrically shaped devices (e.g. hexagon), more than three orientations might be required to address worst case.

Prepare the NIS according to the instructions for use with a new container and proceed as follows.

a) System designations A and B.

   1) Remove the protective cover (e.g. a cap), insert the container, attach the needle and prime or purge the system as required according to the instructions for use.

   2) If removable, remove the needle and replace the cap.

   3) Drop 20 NISs three times by free-fall from a height of 1 000 mm onto the test surface, once horizontally and twice vertically, rotating the system by 180° between the two vertical drops. Care shall be taken to release the system in a non-turbulent way.

4) If a container breaks so that it is completely fractured, replace the container and continue until all three drops have been performed. The number of allowed replacements for each test orientation is three, otherwise the test is considered to have failed.

b) System designations C and D.

1) Remove the protective cover (e.g. a cap), attach a needle and prime or purge the system if required.

2) If removable, take off the needle and put on the cap.

3) Drop the NIS by free-fall from a height of 1 000 mm onto the test surface (see 6.4) in accordance with i), ii) and iii), as follows:

i) horizontal — drop 10 new NISs in a non-turbulent way; if a container breaks so that it is completely fractured in a manner obvious to the user, exclude the system from further testing;

ii) vertical A — drop 10 additional new NISs in a non-turbulent way; if a container breaks so that it is completely fractured in a manner obvious to the user, exclude the system from further testing;

iii) vertical B — [180° from orientation ii)] drop 10 additional new NISs in a non-turbulent way; if a container breaks so that it is completely fractured in a manner obvious to the user, exclude the system from further testing;

iv) the number of allowed replacements for each test orientation is three, otherwise the test is considered to have failed.

c) System designations B1 and B2.

1) Prepare the NIS in accordance with the instructions for use up to the point where sterility is broken.

2) Drop 20 NISs three times by free-fall from a height of 1 000 mm onto the test surface, once horizontally and twice vertically, rotating the system by 180° between the two vertical drops. Care shall be taken to release the system in a non-turbulent way.

3) If a container breaks so that it is completely fractured in a manner obvious to the user, replace the container and continue until all three drops have been performed. The number of allowed replacements for each test orientation is three, otherwise the test is considered to have failed.

d) System designations D1 and D2:

1) Prepare the NIS according to the instructions for use up to the point where sterility is broken.

2) Drop the NIS by free-fall from a height of 1 000 mm onto the test surface (see 6.4) in accordance with i), ii) and iii), as follows:

i) horizontal — drop 10 new NISs in a non-turbulent way; if a container breaks so that it is completely fractured in a manner obvious to the user, exclude the system from further testing;

ii) vertical A — drop 10 additional new NISs in a non-turbulent way; if a container breaks so that it is completely fractured in a manner obvious to the user, exclude the system from further testing;

iii) vertical B — [180° from orientation ii)] drop 10 additional new NISs in a non-turbulent way; if a container breaks so that it is completely fractured in a manner obvious to the user, exclude the system from further testing;

iv) the number of allowed replacements for each test orientation is three, otherwise the test is considered to have failed.

NOTE For system designations C and D, all orientations are combined for dose accuracy assessment.

10.6 Dry-heat and cold-storage testing — Pre-conditioning

Assembled new NISs without containers or needles are placed in a test chamber for at least 96 h in the atmospheres given in Table 5.

Table 5 — Dry-heat and cold-storage temperatures

Condition	Dry heat	Cold storage
Temperature °C	(70 ± 2)	(-40 ± 3)
Humidity %RH	(50 ± 10)	No humidity requirement

System designations C and D that are manufacturer-filled shall be subjected to pre-conditioning at the acceptable high and low storage temperatures, which shall be stated in the instructions for use.

10.7 Damp-heat testing (system designations A and B only) — Pre-conditioning

Assembled new NISs without the containers or needles are placed in a test chamber for at least 96 h in the atmosphere given in Table 6.

Table 6 — Damp heat conditions

Condition	Damp heat
Temperature °C	(40 ± 2)
Humidity %RH	(93 ± 5)

10.8 Cyclical testing (system designations A and B only) — Pre-conditioning

The NIS, with the container and without the needle, shall be conditioned as follows:

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

b) lower temperature of (25 ± 3) °C (no humidity requirement);

c) upper temperature of (55 ± 2) °C and (50 ± 25) %RH;

d) six cycles.

NOTE Further information on the testing chamber, conditioning and recovery can be found in IEC 60068-2-30:2005, Clauses 4, 7 and 9, respectively.

10.9 Vibration testing — Pre-conditioning

Vibrate the NIS with its container and needle in each of the three axes in accordance with IEC 60068-2-6 and Table 7.

Table 7 — Vibration amplitudes with lower crossover frequency

Frequency range	Displacement/acceleration (peak value)	Number of sweeps[a] per direction
3 Hz to 8 Hz	7,5 mm	4
8 Hz to 300 Hz	2g	4
NOTE See Table IV and Figure 1 of IEC 60068-2-6:2007.		
[a] Sweep speed = 1 octave per minute.		

10.10 Electromagnetic compatibility (EMC) (systems with electronics only)

10.10.1 General

NOTE The tests specified in 10.10.2 and 10.10.3 are based on the requirements given in the collateral standard IEC 60601-1-2:2007 for EMC.

The collateral standard IEC 60601-1-2 applies, except as follows.

The requirements given in 10.10.2 and 10.10.3 cancel and replace those specified in IEC 60601-1-2, which only covers requirements for electromedical appliances in general, and does not address specific devices such as NISs.

10.10.2 Exposure to electrostatic discharge — Pre-conditioning

Perform the test in accordance with IEC 60601-1-2:2007, 6.2.2, replacing the test requirements with the following.

Apply contact discharge ±2 kV, ±4 kV and ±8 kV to conductive accessible parts and coupling planes. Apply air discharges ±8 kV, ±10 kV, ±12 kV and ±15 kV to non-conductive accessible parts.

NOTE This subclause overrides ISO 11608-4:2006, 11.1.1, which makes reference to the first edition of this part of ISO 11608.

10.10.3 Radiated radio-frequency (RF) fields — Pre-conditioning

Perform the test in accordance with IEC 60601-1-2:2007, 6.2.3. The test level shall be 10 V/m for the frequency range 26 MHz to 2 500 MHz. Perform the test in each of the three axes of the NIS.

10.10.4 Compliance criteria for electrostatic discharge

Visually inspect the performance (e.g. stored data, settings, dose or indications) of five new NISs with electronic components.

The NISs shall fulfil the following requirements.

a) None of the NISs shall exhibit visible defects after each and all the required electrostatic discharges when tested in accordance with 10.10.2.

b) The performance of the NISs shall not change as a result of the application of the test when evaluated in accordance with the requirements specified in IEC 60601-1-2:2007, 6.2.1.10 and 6.2.1.11. None of the NISs shall have functional defects, as specified in 11.1.

10.10.5 Radiated radio-frequency (RF) fields

Visually inspect the performance (e.g. stored data, settings, dose or indications) of five new NISs with electronic components.

The NISs shall fulfil the following requirements.

a) None of the NISs shall exhibit erroneous indications during the radio-frequency sweep, when tested in accordance with 10.10.3.

b) After application of the radio-frequency sweep, the performance of the NISs shall be inspected. The performance of the NISs shall not change as a result of the application of the test when evaluated in accordance with the requirements specified in IEC 60601-1-2:2007, 6.2.1.10 and 6.2.1.11. None of the NISs shall have functional defects, as specified in 11.1.

11 Inspection

11.1 Visual inspection

Any marking on the NIS that is essential for the safe use of the device shall remain visible, easily legible and indelible after being subjected to pre-conditioning as described in Clause 10. 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. Inspect the NIS for significant defects under normal or corrected-to-normal vision. The inspection should in particular include checking for significant defects such as:

a) markings that are no longer visible or easily legible (that impact safe functioning);

b) cracks in the body and/or component of the NIS that might impact safe functioning;

c) compromised assembly bonds, joints and alignments that might impact safe functioning;

d) for NISs with replaceable batteries, the battery compartment failing to remain closed.

11.2 Container inspection

If the container is completely fractured or has lost its contents in such a way that is obvious to the user, replace the container in order to complete the testing. For system designations C and D, additional samples shall be pre-conditioned to complete the test. Non-obvious damage will be assessed as part of the dose accuracy evaluation.

11.3 Dose accuracy acceptance criteria

A NIS population satisfies the requirements for accuracy when, for a given V_{set}, the following are fulfilled.

Two-sided:

$$\bar{x} + (k \cdot s) \leq U \quad \text{and} \quad \bar{x} - (k \cdot s) \geq L \tag{4}$$

One-sided:

$$\bar{x} - (k \cdot s) \geq L \quad \text{or} \quad \bar{x} + (k \cdot s) \leq U \tag{5}$$

For each V_{set}, k_{act} is analysed according to Equation (6) or (7), based on the specific test and risk assessment.

Two-sided:

$$k_{act} = \min \left[\frac{(U - \bar{x})}{s}, \frac{(\bar{x} - L)}{s} \right] \tag{6}$$

One-sided:

$$k_{act} = \left[\frac{(\bar{x} - L)}{s} \right] \text{ or } \left[\frac{(U - \bar{x})}{s} \right] \tag{7}$$

Then the NIS population satisfies the requirements for accuracy when, for a given V_{set}, the following is fulfilled:

$k_{act} \geq$ target k for the selected probability content and number of measurements

12 Test report

The test report shall be maintained in accordance with ISO 13485:2003, Clause 7. Each test report shall include at least the following information:

a) reference to this part of ISO 11608, i.e. ISO 11608-1:2012;

b) identification of the physical manufacturer (normally the test initiator);

c) identification of the NIS tested;

d) identification of the test system used;

e) identification of the test liquid used;

f) the test results, including a summary of the test conditions used;

g) details of any deviation from this part of ISO 11608,

h) name and address of the test facility;

i) date of the test;

j) dose levels;

k) number of injectors tested.

13 Information supplied by the manufacturer

13.1 General

The NIS shall be accompanied by information that is sufficient for its safe use, taking into account the training and knowledge of potential users. The information shall include the manufacturer's identity.

Instructions for use shall be included in the user packaging.

13.2 Marking

13.2.1 General

Any marking on the user packaging that is essential for the safe use of the NIS 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.

13.2.2 Marking on the NIS

The marking on the NIS shall comprise at least the following particulars:

a) name or trade name of the manufacturer;

NOTE A trademark or logo might be sufficient to identify the manufacturer.

b) details necessary in order for the user to identify the NIS;

c) batch code, lot number or the serial number, preceded by an appropriate symbol.

13.2.3 Marking on the unit packaging

Unless otherwise specified in ISO vertical standards for a specific device, the marking on the unit packaging shall comprise at least the following particulars:

a) name and address of the manufacturer;

b) sufficient details for the user to identify the NIS;

c) content of the unit packaging;

d) information on the type of medicinal product(s) intended to be injected by means of the NIS;

e) batch code, lot number or serial number, preceded by an appropriate symbol;

f) any special storage and/or handling conditions;

g) expiry date, if required (year and month, expressed as YYYY-MM);

EXAMPLE 2008-12.

h) where appropriate, an indication that the NIS is for single use;

i) where provided separately, information on the specific needle(s) and container(s) with which the NIS has been tested.

13.3 Instructions for use

The instructions for use shall contain information on at least the following particulars:

a) information required in 13.2, except for the information regarding the expiry date (if any), lot number, batch code or serial number, which can be omitted;

b) any warnings and/or precautions to be taken, e.g. that the NIS shall not be used for injections if it is obvious to the user that it does not function correctly;

c) any risks associated with its normal use, for example:

   1) NISs with pre-fixed dosages shall only be used by persons able to calculate the number of activations correctly when the injection is performed;

   2) NISs with electronic components shall not be used close to areas of electromagnetic radiation (such as mobile telephones in use) if the NISs are not specially designed to be used in such areas;

d) sufficient details of its characteristics to identify the NIS components and related equipment in order to obtain a safe combination;

e) information on the appropriate process under which re-use of the NIS is allowed, including container replacement, cleaning and disinfection;

f) details of preparation needed before the NIS can be used, for example:

   1) assembly and disassembly of the product, replacement of the container and attachment the needle,

   2) inspection of the container and mixing a suspension,

   3) the need to prime, e.g.

      i) removal of air,

      ii) ensuring contact between plunger and lead screw;

g) description of the method of use, for example:

   1) setting the dose,

   2) reading the residual scale,

   3) step-by-step injection procedure, e.g.

      i) actuation of injection stroke,

      ii) end-of-dose confirmation,

      iii) waiting time before removing the needle from the injection site;

h) dose-setting range;

i) if acceptable, storage temperatures other than those specified in 10.6 [(70 ± 2) °C and (-40 ± 3) °C] and the acceptable temperature range for storage of the NIS without medicinal product;

j) procedure for delivering a dose, when the remaining volume of liquid in the container is less than the volume to be injected;

k) any special storage requirements;

l) type of replaceable batteries and their number, if used;

m) description of special features;

n) whether the NIS is designed so that it

   1) does not allow a larger dose to be pre-set than is left in the container, or

   2) does not allow dose delivery if the pre-set dose exceeds the amount of medicinal product left in the container, or

   3) indicates the amount of medicinal product delivered, or

   4) indicates the amount of medicinal product not delivered of the pre-set dose;

o) general trouble-shooting, for example:

   1) injection force and dose completion issues,

   2) dose correction,

   3) significance of small versus large air bubbles, droplets of liquid at the needle tip;

p) details allowing the medical staff to brief the user on any contra-indications and precautions to be taken (these details should in particular cover precautions to be taken in the event of breakage or changes in the performance of the NIS);

q) precautions to be taken against any special, unusual risks related to the disposal of the system.

Annex A
(informative)

Dose replicates, accuracy and testing rationale

A.1 Dose replicates for variable multi-dose NISs

For a given test, dose accuracy is evaluated by delivering and measuring V_{set} in combinations of injection cycles or replicates (random sequences of the three pre-set doses, V_{set}). A random sequence of three pre-set doses can occur in six possible ways (R_1, R_2, R_3, R_4, R_5 and R_6).

R_1 V_{min}, V_{mid}, V_{max}

R_2 V_{min}, V_{max}, V_{mid}

R_3 V_{mid}, V_{min}, V_{max}

R_4 V_{mid}, V_{max}, V_{min}

R_5 V_{max}, V_{min}, V_{mid}

R_6 V_{max}, V_{mid}, V_{min}

All of these replicates should be tested from each of the three sections of the container, but only one replicate set is taken from each container.

A.2 Accuracy assessment

(Expressed in millilitres)

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

$U = V_{set} + \alpha$;

$L = V_{set} - \alpha$.

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

$U = V_{set} + (\beta \cdot V_{set})/100$;

$L = V_{set} - (\beta \cdot V_{set})/100$.

A NIS population satisfies the requirements for accuracy when, for a given V_{set}, the following are fulfilled (a two-sided example is used):

$$\bar{x} + (k \cdot s) \leq U \quad \text{(A.1)}$$

and

$$\bar{x} - (k \cdot s) \geq L \quad \text{(A.2)}$$

EXAMPLE Dose accuracy tolerance limit calculations.

If V_{set} (DR = 0,01 ml):

V_{min} = 0,01 ml;

V_{mid} = 0,16 ml;

V_{max} = 0,30 ml;

and

α = 0,01 ml;

β = 5 %;

then (expressed in millilitres):

TP = (100 × 0,010 ml)/5 = 0,200

For V_{min} ≤ TP: U = (0,010 + 0,010) = 0,020;

L = (0,010 − 0,010) = 0,000.

For V_{mid} ≤ TP: U = (0,160 + 0,010) = 0,170;

L = (0,160 − 0,010) = 0,150.

For V_{max} > TP: U = 0,300 + (5 × 0,300 ml)/100 = 0,315;

L = 0,300 × (5 × 0,300 ml)/100 = 0,285.

A.3 Test rationale

A.3.1 Standard, cool and warm atmosphere testing

These tests are intended to measure the performance of the injector across a temperature and humidity range that can be reasonably associated with "in-use" environments, such as controlled and uncontrolled indoor and outdoor conditions. Outdoor conditions encompass seasonal (winter to summer) variations and indoor conditions encompass the year-round variations in "room temperature". This part of ISO 11608 does not allow for the manufacturer to change the test conditions as it is not reasonable to expect that "in-use" conditions can be controlled through labelling.

A.3.2 Last-dose accuracy testing

The last dose is considered as important as any other dose and should therefore meet the same accuracy requirements, barring specific allowances determined by the risk assessment. However, based on device design, testing last-dose accuracy can be problematic and might require different methods, particularly for devices that permit the setting of doses greater than the remaining volume, where the last dose cannot be known exactly prior to dose delivery. Therefore, this test provides special consideration for the last dose to accommodate the unique statistical challenge in calculating accuracy when last-dose volumes cannot be predicted or known exactly.

A.3.3 Life-cycle testing

Life-cycle testing is intended to verify the in-use performance of the NIS after the delivery of 1,5 times the maximum number of actuations expected during its lifetime. 1,5 provides a reasonable safety factor above the expected duty cycle of the NIS. This test does not address storage during the period of time between manufacture and first use by the patient.

A.3.4 Free-fall testing

Free-fall testing is intended to verify the performance of the NIS after impact when dropped in its ready-to-use condition without external packaging (or carrying cases). These devices are tested in a condition consistent with that in which they would be taken from their place of storage in preparation for use. Devices are tested with the container installed, without a needle (if removable) and with a cap (if provided). Multi-dose devices are primed (with removal of the needle and replacement of the cap) as representing its most common ready-to-use condition. Single-dose devices are assembled and prepared to the point prior to sterility being broken. No other process (arming, unlocking, dose setting, etc.) would be performed.

A nominal height of 1 m is used (this is a likely height at which the device would be held or kept on a table top). System designation A and B devices are tested from multiple orientations while system designations C and D are tested from only one orientation due to their limited in-use life. The test accommodates the possibility that some glass containers might break upon impact due to their fragility. In most cases, this failure will be evident to the user and the user will replace the cartridge or the entire pen.

While it is understood that the device cannot provide absolute protection for the primary container, it should provide some protection. Therefore, independent of whether the failure is evident to the user, if there are more than three failures in any one orientation, the test is considered to have failed. Additionally, instances where the container damage is not evident to the user (e.g. micro-cracks jeopardizing drug sterility or secondary liquid paths) are considered to have failed as a function of the visual and functional investigation. All other failures of the device to operate as intended are considered failures.

A.3.5 Dry-heat and cold-storage testing

These tests are intended to measure the performance of the injector after exposure to extreme hot and cold storage and shipping conditions as well as potential extreme user interactions (e.g. placing the device on a car dashboard in hot weather or accidentally storing the device in the freezer).

These test conditions may be modified if the manufacturer actively controls the shipping and storage conditions of the product and if the labelled shipping and storage conditions are consistent with those used in the testing. This is usually done when the drug is supplied manufacturer-filled, or in the same package as the injection device, and when the drug requires controlled shipping and storage conditions to ensure potency and stability. Similarly, modifications to the test conditions may be supported for all products where materials and/or components cannot tolerate these extremes and where the use of these materials is justified and documented in the risk assessment.

Even if the labelling is modified and the verification tests are carried out under different conditions, testing products at these extremes can provide additional value in understanding the ultimate device performance. It may also be helpful in assessing potential excursions from controlled storage and shipping conditions across the supply chain.

A.3.6 Damp-heat testing

This test is intended to measure the performance of the injector after exposure to the same dry-heat test temperature, but at much higher humidities. This type of test is sometimes referred to as a “soak” in that the moisture level associated with high humidity can have a material impact on device components, including the electronics.

While not required for system designations C and D, which are manufacturer-filled to protect the medicinal product, this test is still recommended for all products in order to assess the robustness of the injector design. It is also understood that many components and subassemblies will be shipped and stored under uncontrolled conditions; this test will help identify any potential issues.

A.3.7 Cyclical atmosphere testing

This test is intended to apply stress to the device design. The test conditions (adapted from an IEC electro-mechanical standard) are designed to determine the suitability of materials and components for use, and transportation and storage under conditions of high humidity, combined with cyclic temperature changes which can produce condensation on the surface of the device components. While the formation of condensation is of particular interest for electronic devices, the impact of condensation (e.g. the impact of condensation on the

ability to view the dose number through a dose window lens), expansion and contraction due to the extreme temperature changes is applicable to all devices.

While not required for system designations C and D, which are manufacturer-filled to protect the medicinal product, this test is still recommended for all products in order to assess the robustness of the injector design. It is also understood that many components and subassemblies will be shipped and stored under uncontrolled conditions; this test will help identify any potential issues.

A.3.8 Vibration testing

Vibration testing is intended to simulate ambulatory patient storage such as when a patient carries the device for use during the day (e.g. on public transport or when running). As such, this test is for all devices (not just electromechanical) and is performed on the device without packaging.

A.3.9 Electrostatic discharge testing

Electrostatic discharge testing is intended to verify the integrity of the NIS after exposure to electrostatic discharge, both through contact and non-contact, which might occur during normal patient transport and during use of the device. This test is applicable only to devices with electronics.

A.3.10 Radio-frequency (RF) interference

RF field testing is intended to verify the integrity of the NIS after exposure to RF interference, which might occur during normal patient transport and during use of the device. This test is applicable only to devices with electronics.

Annex B
(normative)

One- and two-sided tolerance limit factors, k

Table B.1 — One-sided tolerance limit factors

Gamma = 0,950							
N	p = 0,750	p = 0,900	p = 0,950	p = 0,975	p = 0,990	p = 0,999	p = 0,999 9
2	11,763	20,581	26,260	31,257	37,094	49,276	59,304
3	3,806	6,155	7,656	8,986	10,553	13,857	16,598
4	2,618	4,162	5,144	6,015	7,042	9,214	11,019
5	2,150	3,407	4,203	4,909	5,741	7,502	8,966
6	1,895	3,006	3,708	4,329	5,062	5,512	7,901
7	1,732	2,755	3,399	3,970	4,642	6,063	7,244
8	1,618	2,582	3,187	3,723	4,354	5,688	6,796
9	1,532	2,454	3,031	3,542	4,143	5,413	6,469
10	1,465	2,355	2,911	3,402	3,981	5,203	6,219
11	1,411	2,275	2,815	3,292	3,852	5,036	6,020
12	1,366	2,210	2,736	3,201	3,747	4,900	5,858
13	1,328	2,155	2,671	3,125	3,659	4,787	5,723
14	1,296	2,109	2,614	3,060	3,585	4,690	5,609
15	1,268	2,068	2,566	3,005	3,520	4,607	5,510
16	1,243	2,033	2,524	2,956	3,464	4,535	5,424
17	1,220	2,002	2,486	2,913	3,414	4,471	5,348
18	1,201	1,974	2,453	2,875	3,370	4,415	5,281
19	1,183	1,949	2,423	2,841	3,331	4,364	5,221
20	1,166	1,926	2,396	2,810	3,295	4,318	5,167
21	1,152	1,905	2,371	2,781	3,263	4,277	5,118
22	1,138	1,886	2,349	2,756	3,233	4,239	5,073
23	1,125	1,869	2,328	2,732	3,206	4,204	5,031
24	1,114	1,853	2,309	2,710	3,181	4,172	4,994
25	1,103	1,838	2,292	2,690	3,158	4,142	4,959
26	1,093	1,824	2,275	2,672	3,136	4,115	4,926
27	1,083	1,811	2,260	2,654	3,116	4,089	4,896
28	1,075	1,799	2,246	2,638	3,098	4,066	4,868
29	1,066	1,788	2,232	2,623	3,080	4,043	4,841
30	1,058	1,777	2,220	2,608	3,064	4,022	4,816

Table B.1 *(continued)*

Gamma = 0,950							
N	$p = 0{,}750$	$p = 0{,}900$	$p = 0{,}950$	$p = 0{,}975$	$p = 0{,}990$	$p = 0{,}999$	$p = 0{,}999\ 9$
31	1,051	1,767	2,208	2,595	3,048	4,002	4,793
32	1,044	1,758	2,197	2,582	3,034	3,984	4,771
33	1,037	1,749	2,186	2,570	3,020	3,966	4,750
34	1,031	1,740	2,176	2,559	3,007	3,950	4,730
35	1,025	1,732	2,167	2,548	2,995	3,934	4,712
36	1,019	1,725	2,158	2,538	2,983	3,919	4,694
37	1,014	1,717	2,149	2,528	2,972	3,904	4,677
38	1,009	1,710	2,141	2,518	2,961	3,891	4,661
39	1,004	1,704	2,133	2,510	2,951	3,878	4,646
40	0,999	1,697	2,125	2,501	2,941	3,865	4,631
41	0,994	1,691	2,118	2,493	2,932	3,854	4,617
42	0,990	1,685	2,111	2,485	2,923	3,842	4,603
43	0,986	1,680	2,105	2,478	2,914	3,831	4,591
44	0,982	1,674	2,098	2,470	2,906	3,821	4,578
45	0,978	1,669	2,092	2,463	2,898	3,811	4,566
46	0,974	1,664	2,086	2,457	2,890	3,801	4,555
47	0,971	1,659	2,081	2,450	2,883	3,792	4,544
48	0,967	1,654	2,075	2,444	2,876	3,783	4,533
49	0,964	1,650	2,070	2,438	2,869	3,774	4,523
50	0,960	1,646	2,065	2,432	2,862	3,766	4,513
51	0,957	1,641	2,060	2,427	2,856	3,758	4,504
52	0,954	1,637	2,055	2,421	2,850	3,750	4,494
53	0,951	1,633	2,051	2,416	2,844	3,742	4,485
54	0,948	1,630	2,046	2,411	2,838	3,735	4,477
55	0,945	1,626	2,042	2,406	2,833	3,728	4,468
56	0,943	1,622	2,038	2,401	2,827	3,721	4,460
57	0,940	1,619	2,034	2,397	2,822	3,714	4,452
58	0,938	1,615	2,030	2,392	2,817	3,708	4,445
59	0,935	1,612	2,026	2,388	2,812	3,701	4,437
60	0,933	1,609	2,022	2,384	2,807	3,695	4,430
61	0,930	1,606	2,019	2,380	2,802	3,689	4,423
62	0,928	1,603	2,015	2,376	2,798	3,684	4,416
63	0,926	1,600	2,012	2,372	2,793	3,678	4,410
64	0,924	1,597	2,008	2,368	2,789	3,673	4,403
65	0,921	1,594	2,005	2,364	2,785	3,667	4,397
66	0,919	1,591	2,002	2,361	2,781	3,662	4,391
67	0,917	1,589	1,999	2,357	2,777	3,657	4,385
68	0,915	1,586	1,996	2,354	2,773	3,652	4,379
69	0,913	1,584	1,993	2,351	2,769	3,647	4,373

Table B.1 *(continued)*

Gamma = 0,950							
N	p = 0,750	p = 0,900	p = 0,950	p = 0,975	p = 0,990	p = 0,999	p = 0,999 9
70	0,911	1,581	1,990	2,347	2,765	3,643	4,368
71	0,910	1,579	1,987	2,344	2,762	3,638	4,362
72	0,908	1,576	1,984	2,341	2,758	3,633	4,357
73	0,906	1,574	1,982	2,338	2,755	3,629	4,352
74	0,904	1,572	1,979	2,335	2,751	3,625	4,347
75	0,903	1,570	1,976	2,332	2,748	3,621	4,342
76	0,901	1,568	1,974	2,329	2,745	3,617	4,337
77	0,899	1,565	1,971	2,327	2,742	3,613	4,333
78	0,898	1,563	1,969	2,324	2,739	3,609	4,328
79	0,896	1,561	1,967	2,321	2,736	3,605	4,323
80	0,895	1,559	1,964	2,319	2,733	3,601	4,319
81	0,893	1,557	1,962	2,316	2,730	3,597	4,315
82	0,892	1,556	1,960	2,314	2,727	3,594	4,310
83	0,890	1,554	1,958	2,311	2,724	3,590	4,306
84	0,889	1,552	1,956	2,309	2,721	3,587	4,302
85	0,888	1,550	1,954	2,306	2,719	3,583	4,298
86	0,886	1,548	1,952	2,304	2,716	3,580	4,294
87	0,885	1,547	1,950	2,302	2,714	3,577	4,291
88	0,884	1,545	1,948	2,300	2,711	3,574	4,287
89	0,882	1,543	1,946	2,297	2,709	3,571	4,283
90	0,881	1,542	1,944	2,295	2,706	3,567	4,279
91	0,880	1,540	1,942	2,293	2,704	3,564	4,276
92	0,879	1,538	1,940	2,291	2,701	3,561	4,272
93	0,877	1,537	1,938	2,289	2,699	3,559	4,269
94	0,876	1,535	1,937	2,287	2,697	3,556	4,266
95	0,875	1,534	1,935	2,285	2,695	3,553	4,262
96	0,874	1,532	1,933	2,283	2,692	3,550	4,259
97	0,873	1,531	1,931	2,281	2,690	3,547	4,256
98	0,872	1,530	1,930	2,279	2,688	3,545	4,253
99	0,871	1,528	1,928	2,278	2,686	3,542	4,250
100	0,870	1,527	1,927	2,276	2,684	3,539	4,247
102	0,868	1,524	1,923	2,272	2,680	3,534	4,241
104	0,866	1,521	1,920	2,269	2,676	3,530	4,235
106	0,864	1,519	1,917	2,266	2,672	3,525	4,229
108	0,862	1,517	1,915	2,262	2,669	3,520	4,224
110	0,860	1,514	1,912	2,259	2,665	3,516	4,219
112	0,858	1,512	1,909	2,256	2,662	3,511	4,214
114	0,856	1,510	1,907	2,253	2,658	3,507	4,209
116	0,855	1,507	1,904	2,251	2,655	3,503	4,204
118	0,853	1,505	1,902	2,248	2,652	3,499	4,199

Table B.1 *(continued)*

Gamma = 0,950							
N	$p = 0{,}750$	$p = 0{,}900$	$p = 0{,}950$	$p = 0{,}975$	$p = 0{,}990$	$p = 0{,}999$	$p = 0{,}999\ 9$
120	0,851	1,503	1,899	2,245	2,649	3,495	4,195
122	0,850	1,501	1,897	2,242	2,646	3,492	4,190
124	0,848	1,499	1,895	2,240	2,643	3,488	4,186
126	0,847	1,497	1,893	2,237	2,640	3,484	4,182
128	0,845	1,496	1,890	2,235	2,638	3,481	4,178
130	0,844	1,494	1,888	2,233	2,635	3,478	4,174
132	0,843	1,492	1,886	2,230	2,632	3,474	4,170
134	0,841	1,490	1,884	2,228	2,630	3,471	4,166
136	0,840	1,489	1,882	2,226	2,627	3,468	4,162
138	0,839	1,487	1,880	2,224	2,625	3,465	4,159
140	0,837	1,485	1,879	2,222	2,622	3,462	4,155
142	0,836	1,484	1,877	2,220	2,620	3,459	4,152
144	0,835	1,482	1,875	2,218	2,618	3,456	4,148
146	0,834	1,481	1,873	2,216	2,616	3,453	4,145
148	0,833	1,479	1,872	2,214	2,613	3,451	4,142
150	0,832	1,478	1,870	2,212	2,611	3,448	4,139
152	0,830	1,476	1,868	2,210	2,609	3,445	4,136
154	0,829	1,475	1,867	2,208	2,607	3,443	4,133
156	0,828	1,474	1,865	2,207	2,605	3,440	4,130
158	0,827	1,472	1,864	2,205	2,603	3,438	4,127
160	0,826	1,471	1,862	2,203	2,601	3,435	4,124
162	0,825	1,470	1,861	2,201	2,600	3,433	4,121
164	0,824	1,469	1,859	2,200	2,598	3,431	4,118
166	0,823	1,467	1,858	2,198	2,596	3,428	4,116
168	0,822	1,466	1,856	2,197	2,594	3,426	4,113
170	0,822	1,465	1,855	2,195	2,592	3,424	4,111
172	0,821	1,464	1,854	2,194	2,591	3,422	4,108
174	0,820	1,463	1,852	2,192	2,589	3,420	4,106
176	0,819	1,462	1,851	2,191	2,587	3,418	4,103
178	0,818	1,460	1,850	2,189	2,586	3,416	4,101
180	0,817	1,459	1,849	2,188	2,584	3,414	4,098
185	0,815	1,457	1,846	2,185	2,580	3,409	4,093
190	0,813	1,454	1,843	2,181	2,577	3,404	4,087
195	0,811	1,452	1,840	2,178	2,573	3,400	4,082
200	0,809	1,450	1,837	2,175	2,570	3,395	4,077
205	0,808	1,447	1,835	2,172	2,566	3,391	4,072
210	0,806	1,445	1,832	2,170	2,563	3,387	4,068
215	0,804	1,443	1,830	2,167	2,560	3,384	4,063
220	0,803	1,441	1,828	2,164	2,557	3,380	4,059