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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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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”.