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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.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT), see www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 84, *Devices for administration of medicinal products and catheters,* in collaboration with the European Committee for Standardization (CEN) Technical Committee CEN/TC 205, *Non-active medical devices,* in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

This fourth edition cancels and replaces the third edition (ISO 11608-1:2014), which has been technically revised.

The main changes are as follows:

— relocation of content to the other parts of the ISO 11608 series, as appropriate (see Figure 1);

— added language to address the case when a platform NIS is applied for different therapeutics or users;

— clarified that the “user” referenced in this document is the patient receiving the therapeutic, and not the health care professional who prescribes the medication (see Clause 1);

— defined “bolus”, and confirmed that this document is focused on bolus (fixed dose) delivery (not basal bolus), so as to distinguish from the definition in IEC 60601-2-24 (see Clause 1);

— clarified the references to ISO 13485, ISO 14971 and IEC 62366-1 (see 5.1.2, 5.3 and 5.4, respectively) and exclude any reference to an equivalent standard;

— elimination of the term “essential performance” and defined “primary functions” - those functions for which failure would “directly” result in “new and unacceptable harm”. This is to eliminate confusion with use of the term essential performance in IEC 60601-1 (see 5.7.2, Clause 7 and Annex H). Further, there is a focus on “unacceptable harm” and not just “risk”;

— clarification of the recommendations for sample sizes for primary functions (Clause 7), simplified the number of rules from 3 to 2 (see 7.4.2.1), and updated the recommended sample sizes (see Table 3), but confirmed that different sample sizes can be chosen, if justified [see Clause 9 g)];

— the rationale for different sample sizes for free fall testing between system designations A/B and C/D was clarified (see 10.3.1 and Annex A);

— differentiated lighting levels for user legibility – the ability of the user to read the labelling in normal use conditions (see 11.2) and inspection for defects (see 11.3);

— rationales in Annex A were expanded to address clauses throughout the document.

A list of all parts in the ISO 11608 series can be found on the ISO website.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

This document covers needle-based injection systems (referred to as NISs) intended for human use. It provides performance requirements and characteristics so that variations of design are not unnecessarily restricted. The document does not cover needle-free injectors.

Because of the anticipated variation in the designs of NISs, this document tends to specify the results of the design effort instead of the physical and construction requirements used as the basis for NIS design.

The ISO 11608 series deals with "hand-held" or "on-body" delivery systems (OBDSs). By hand-held, users (patients or caregivers) control and stabilize the NIS at the injection site during administration of a discrete volume. Delivery times for this type of NIS would, therefore, be limited to avoid instability and the potential for injection site trauma. For NISs with larger delivery volumes or physical properties requiring a longer time to deliver, OBDS might be more practical. The OBDS would likely exist as either "body-worn" (directly anchored to the body, e.g. using adhesive) or "patient-worn" (indirectly anchored, e.g. catheter attached to OBDS contained in a back-pack or pocket). In either configuration, the time or speed employed to deliver a discrete volume would be based upon tolerability or convenience rather than clinical relevance (e.g. medication efficacy) as would be the case with insulin patch pumps or traditional infusion pumps (e.g. IEC 60601-2-24, ISO 28620) associated with continuous delivery (e.g. insulin). However, while this document is not intended to directly apply to these pump products, it does contain requirements and tests methods that can be used to help design and evaluate them.

The ISO 11608 series includes requirements for design verification of the NIS's conformance with its design specification. The sampling plans, preconditioning criteria and other aspects of testing specified in these documents are intended to verify the design at a high confidence level. They are not intended to stipulate lot release acceptance criteria (AQL, *p*-content, probability, etc.) associated with a manufacturing process. The ISO 11608 series includes other aspects beyond dose accuracy. Finally, it develops the requirement for functional stability and offers additional statistical approaches (e.g. use of variable and attribute data) in satisfying the various NIS design verification requirements.

Figure 1 illustrates the correlations between the different parts in the ISO 11608 series and other applicable standards.

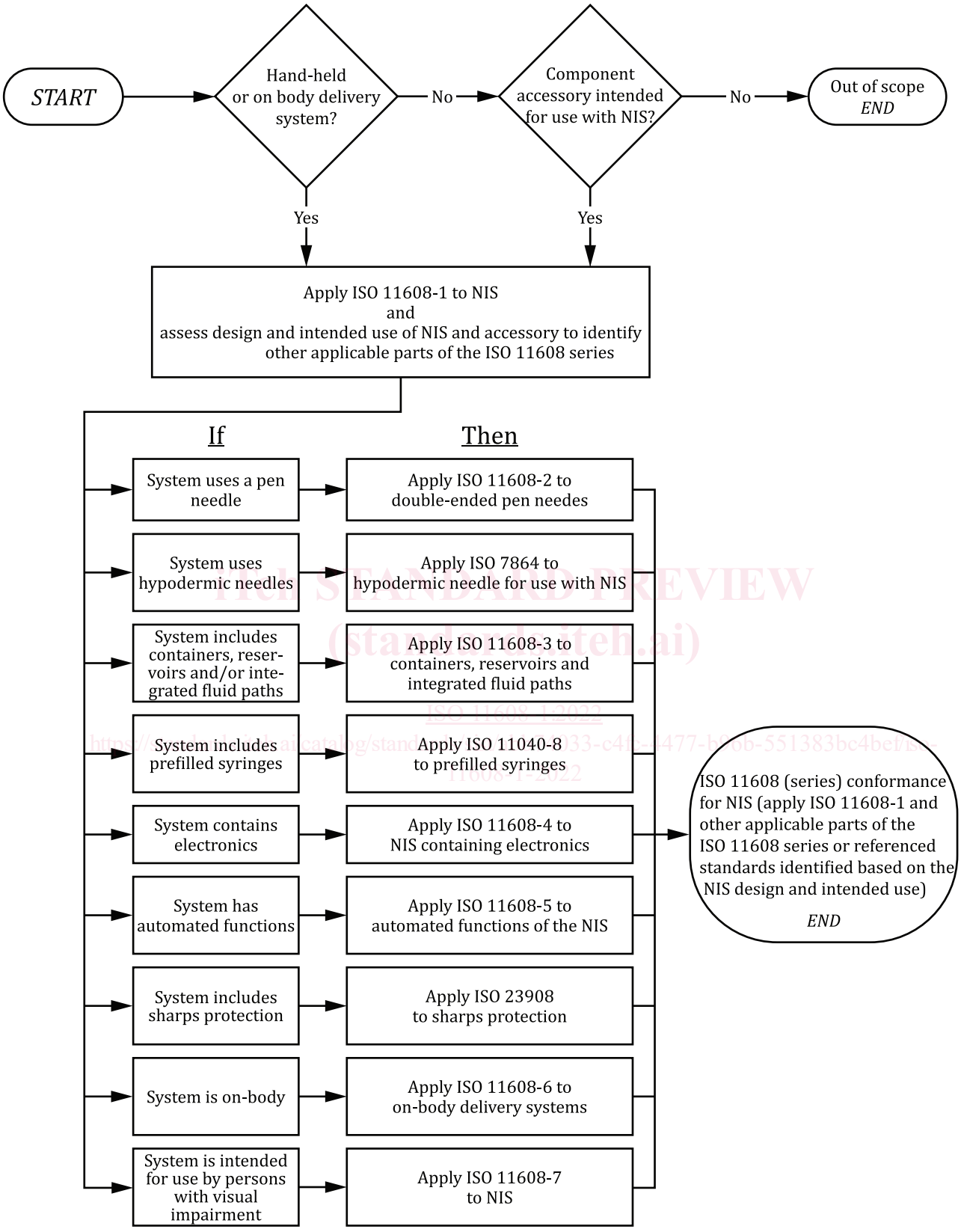

Figure 1 — ISO 11608 series road map

The design requirements related to system function are presented as to assist manufacturers during the design phase. However, these design requirements do not replace system testing of the components

and, where possible, direct communication and/or quality agreements between system component manufacturers.

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, guidance publications and, in some countries, national regulations that are applicable to medical devices and pharmaceuticals. Developers and manufacturers of NISs are encouraged to investigate and determine whether there are any other requirements relevant to the suitability and safety of their products.

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

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

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

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

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

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

Part 1: Needle-based injection systems

1 Scope

This document specifies requirements and test methods for Needle-Based Injection Systems (NISs) for single-patient use intended to deliver discrete volumes (bolus) of medicinal product, which can be delivered through needles or soft cannulas for intradermal, subcutaneous and/or intramuscular delivery, incorporating pre-filled or user-filled, replaceable or non-replaceable containers.

This document applies in cases where the NIS incorporates a prefilled syringe. However, stand-alone prefilled syringes defined by ISO 11040-8 are not covered by this document (see exclusions below).

It is important to note that other functions and characteristics of the prefilled syringe, such as dose accuracy, are subject to the requirements (delivered volume) in ISO 11040-8 and not this document, unless the addition impacts the delivery function (e.g. a mechanism that intends to restrict or stop the plunger movement, which would limit the dose delivered). In that case, the system is completely covered by this document and applicable requirements of the ISO 11608 series.

Excluded from the scope are:

— stand-alone prefilled syringes defined by ISO 11040-8 (with noted exceptions above);

— NISs that provide continuous delivery and require a delivery rate clinically specified in the medicinal product labelling or determined by a physician based on clinical relevance (i.e. medication efficacy) as would be the case with insulin patch pumps or traditional infusion pumps (e.g. IEC 60601-2-24, ISO 28620) associated with continuous delivery of medicinal products (e.g. insulin);

— NISs with containers that can be refilled multiple times;

— requirements relating to methods or equipment associated with user filling of containers unless they are dedicated accessories (a component necessary for primary function, whether included in the original kitted product or not);

— NISs intended for dental use;

— NISs intended for different routes of administration (e.g. intravenous, intrathecal, intraocular).

NOTE These products that are excluded might benefit from elements in this document but might not completely fulfil the basic safety and effectiveness of such products.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

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

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

ISO 16269-6, *Statistical interpretation of data — Part 6: Determination of statistical tolerance intervals*

ISO 23908, *Sharps injury protection — Requirements and test methods — Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling*

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

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

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

3 Terms and definitions

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

ISO and IEC maintain terminology databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at https://www.electropedia.org/

3.1
accessory
article or supplementary part used in conjunction with a *needle-based injection system* (3.15)

3.2
bolus
discrete quantity of medicinal product

3.3
container
component(s) of the *needle-based injection system* (3.15) used to hold the medicinal product

Note 1 to entry: Containers can be integrated into the *needle-based injection system* (3.15) at the point of manufacture or assembled into the *needle-based injection system* (3.15) at the time of use.

Note 2 to entry: The container can be the *primary container closure* (3.17) if provided pre-filled by the manufacturer or a *reservoir* (3.20) if filled at the time of use.

3.4
deliverable volume
contents of the *container* (3.3) that can be expelled by operating the *needle-based injection system* (3.15) in according to the *instructions for use* (3.10)

Note 1 to entry: Deliverable volume can be less than the fill volume.

3.5
design specification
functional, performance, usability or safety characteristic of a *needle-based injection system* (3.15), developed from design inputs, that is confirmed during design verification

Note 1 to entry: The focus of this document is design verification; it does not specify how to perform design validation.

3.6
dose delivery efficiency
ratio of expelled volume to fill volume

Note 1 to entry: Delivery efficiency can be used to evaluate *dose accuracy* (3.7) for *needle-based injection systems* (3.15) designed to fully empty single-dose *containers* (3.3) filled by the user.

3.7
dose accuracy
difference between the intended dose and the delivered dose

3.8
fluid path
pathway the medicinal product follows from the *container* (3.3) to the targeted delivery site

Note 1 to entry: This can include a *reservoir* (3.20).

3.9
functional stability
ability of a *needle-based injection system* (3.15) to maintain its *primary function* (3.18) over a specified period of time and/or number of actuations

Note 1 to entry: See Annex D for further information.

3.10
instructions for use
IFU
directions provided by the manufacturer for the correct handling and operation of the *needle-based injection system* (3.15)

3.11
intended dose
amount of medicinal product intended to be delivered at one time

3.12
in-use life
period of time or number of actuations during which the *needle-based injection system* (3.15) maintains *primary functions* (3.18), when used according to the *instructions for use* (3.10)

Note 1 to entry: For system designations A and B, this might be defined by battery life, total number of doses delivered or a combination of these or other factors.

Note 2 to entry: For system designations C and D from first breach of sterility/*primary container closure* (3.17) through its last dose delivered.

3.13
manufacturer-filled
pre-filled with the medicinal product by the manufacturer

Note 1 to entry: See also *primary container closure* (3.17). See ISO 11608-3:2022, Annex F.

Note 2 to entry: This medicinal product can be in liquid form or lyophilized form with diluent.

3.14
minimum deliverable dose
for *needle-based injection system* (3.15) with system designations B1 and D1 filled by the manufacturer, the minimum dose the system is capable of delivering

3.15
needle-based injection system
NIS
injection system intended for parenteral administration of medicinal products using a needle or cannula and a multi-dose or single-dose container

3.16
pre-set dose
individual amount of medicinal product selected for injection ahead of the use of the *needle-based injection system* (3.15)

Note 1 to entry: The doses can be pre-set by the manufacturer or the user.

3.17
primary container closure
PCC
container (3.3) in direct contact with the medicinal product whose primary purpose is to contain and protect the medicinal product during transportation, storage and use

Note 1 to entry: The PCC is *manufacturer-filled* (3.13).

3.18
primary function
function or operation of the *needle-based injection system* (3.15), which, if it does not perform to specifications during use, would directly result in a failure to accurately deliver the medicinal product via the correct route and/or directly result in unacceptable harm to the patient

Note 1 to entry: At a minimum, this includes the dose delivery function, achieved through assessment of *dose accuracy* (3.7). See also 5.7.2.

Note 2 to entry: Primary function is related to the definition of "essential performance" in IEC 60601-1, but differs in the following ways:

— accurate delivery of the medicinal product via the correct route, i.e. clinical function, independent of the potential for harm to the patient; and

— functions and operations where a failure can cause a situation where the product can directly cause unacceptable harm to the patient, even if these would be considered “basic safety” in IEC 60601-1.

Note 3 to entry: See Annex H.

3.19
priming
actions that make the dosing mechanism of the *needle-based injection system* (3.15) ready for use

EXAMPLE Removing air from the fluid path.

3.20
reservoir
container (3.3) supplied empty that is in direct contact with the medicinal product once filled by the user

Note 1 to entry: The reservoir's primary purpose is to contain the medicinal product prior to the initiation of delivery.

Note 2 to entry: See ISO 11608-3:2022, Annex F.

3.21
residual volume
volume of medicinal product remaining within the *needle-based injection system* (3.15), after dose delivery has been completed

Note 1 to entry: In the case of a *needle-based injection system* (3.15) that incorporates a connecting pathway to a separate, non-integral needle or cannula, the residual volume will include the volume within the said connecting pathway [this applies to both single-use and re-usable *needle-based injection systems* (3.15)].

3.22
residual scale
scale that indicates the remainder of medicinal product in the *container* (3.3)

3.23
shelf life
maximum length of time (usually measured in months or years) from the point of manufacture to release into the supply chain up to the point of first use

3.24
system designation
means of delineating different types of *needle-based injection system* (3.15) by whether the (medication) *container* (3.3) is replaceable or non-replaceable, and if that container is intended to contain multiple doses or a single dose

Note 1 to entry: See Table 1 for system designations.

3.25
user-filled
filled via a manual or automated process by the user from a separate medicinal product or diluent container, or reconstituted (e.g. if in lyophilized form)

4 Symbols

P_{meas}	Measured value of parameter of interest other than dose accuracy
P_{set}	Parameter of interest other than dose accuracy (e.g. dialling torque)
V_{set}	One of any pre-set doses (expressed as a volume, in millilitres) used in determining the dose accuracy for a given NIS
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 NISs required for a given test
R	Replicate, a random sequence of different dose volumes tested
n	Number of measurements
$\bar{x}$	The sample mean; when based on a random sample, an estimate of the true mean
s	The sample standard deviation; when based on a random sample, an estimate of the true standard deviation
k	k value, or tolerance limit factor, determined from the confidence level (95 %), probability content, p, and number of measurements, n, conducted. The k-value is found in Annex B
R_D	Dialling resolution, the minimum dose setting 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
P_T	The transition point volume, in millilitres, at which the upper and lower specification limits for V_{set} change from absolute terms to relative terms: