INTERNATIONAL STANDARD

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Fourth edition
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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)];

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— 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.

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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.

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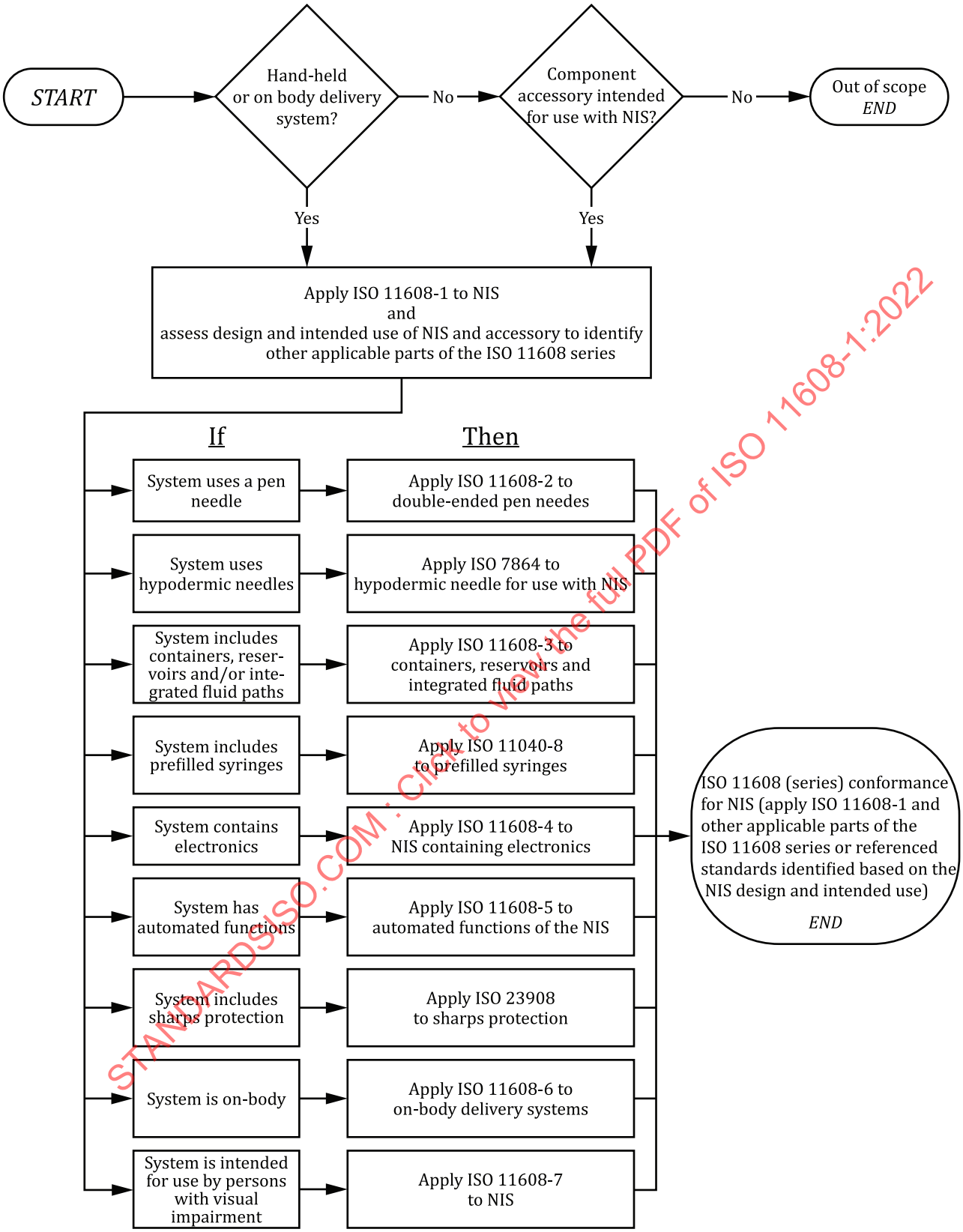

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Figure 1 — ISO 11608 series road map

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

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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.

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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*

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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.

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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

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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)

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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:

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

P_{USL} Upper specification limit for a given P_{set}

P_{LSL} Lower specification limit for a given P_{set}

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

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

5 Requirements

5.1 General

5.1.1 This document addresses requirements for the NIS as a system.

5.1.2 For the design and development of the NIS, a QMS such as ISO 13485:2016, 7.3 can be used.

5.1.3 Prior to design verification, the manufacturer shall establish the NIS design specification by considering the characteristics required for both the NIS (e.g. actuation spring force, material selection) and medicinal product (e.g. shear, formulation viscosity, storage temperature, expiration dating). Once the design specification is established and representative samples have been fabricated, NIS design verification, in accordance with this document, shall be conducted.

Figure 2 represents the relationship of this document with the design and development processes.

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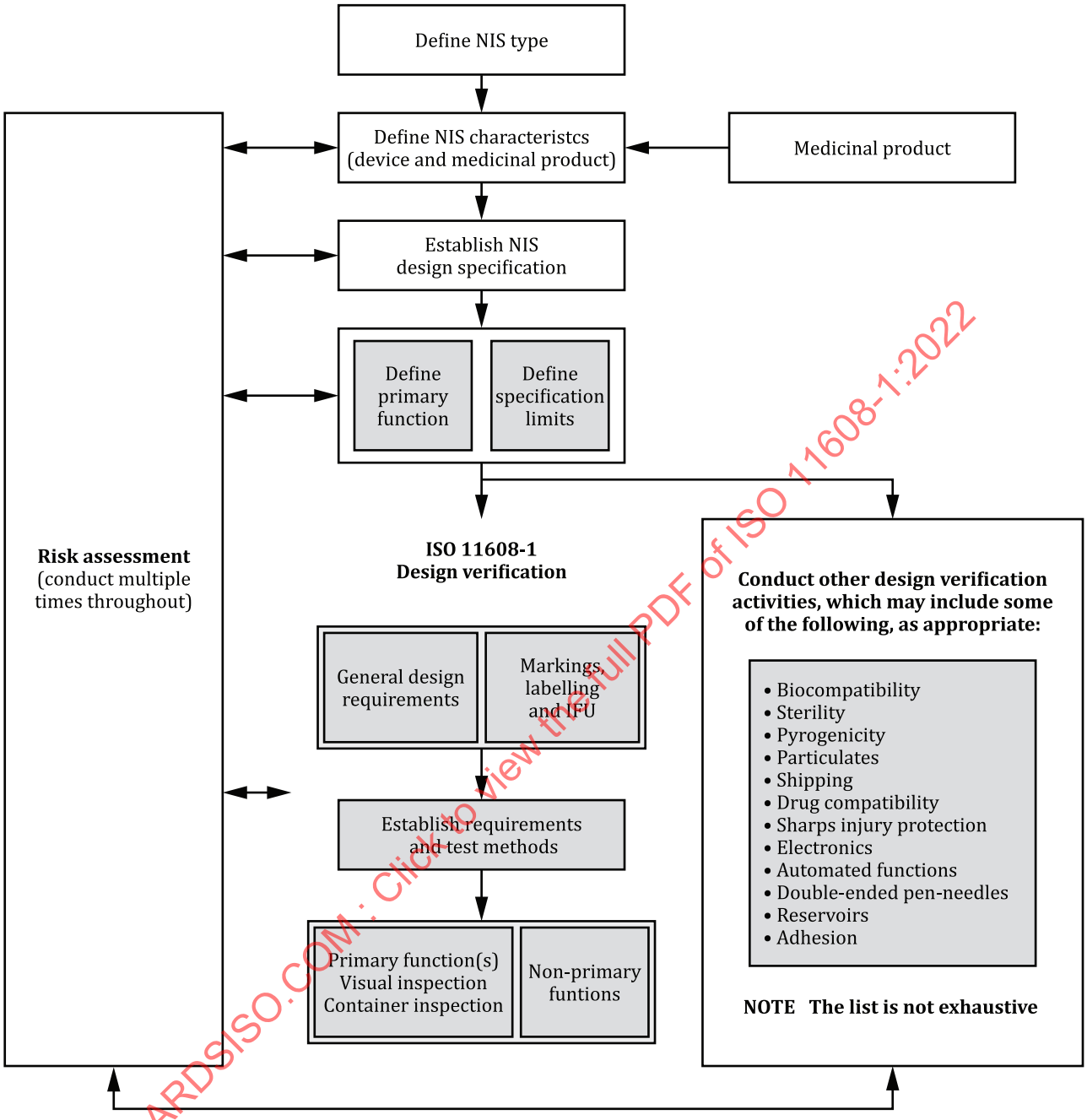

Figure 2 — Design verification flow

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5.1.4 The manufacturer shall confirm that the materials of construction are appropriate for use by the intended user population and materials selected are compatible with the medicinal product.

NOTE Assessment of compatibility of materials of construction is addressed in other documents.

5.2 System designations

Given the differences in NIS 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 NIS system designations.

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Table 1 — System designations

	Multi-dose container	Single-dose container
NIS with replaceable container	A Each container holds multiple doses, the size of which may be fixed or variable (set by the user)	B1 Each container holds a single dose, and the entire deliverable volume is expelled
		B2 Each container holds a single dose, and a portion of the deliverable volume is expelled
NIS with non-replaceable container which is integrated, or user assembled	C The container holds multiple doses, the size of which may be fixed or variable (set by the user)	D1 The container holds a single dose, and the entire deliverable volume is expelled
		D2 The container holds a single dose, and a portion of the deliverable volume is expelled

5.3 Risk approach

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

NOTE 1 Given that many of the NIS products covered in this document will be assessed as a unique system (i.e. medicinal product-device combination product), there will be instances where relevant requirements, specifications, methods or limits will not be specified in the ISO 11608 series. Additionally, those that are specified might not be directly applicable and/or appropriate for the NIS product being assessed.

Risk management tools shall be used to accomplish the following:

— identify primary functions of the system in relation to the intended use of the NIS;

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

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

NOTE 2 For additional understanding about risk approach, see Introduction.

NOTE 3 Risk approach can include foreseeable "worst case" NIS use-cases (e.g. NIS regularly carried by user, versus being stored until immediately before use), conditions, requirements, or configurations (e.g. wear position, NIS orientation).

5.4 Usability engineering

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

5.5 Uncertainty of measurement and conformance with specifications

Uncertainty of measurement shall be evaluated and expressed.

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

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In addition, 6.1 provides specific requirements for the repeatability and reproducibility of the test apparatus for the measurement of primary functions of the NIS.

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

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

5.6 General design requirements

a) Medicinal product shall be visible prior to use of the NIS (e.g. before use, during preparation steps, etc.) to enable inspection.

   If any reconstitution or mixing of compounds is required to prepare the NIS for operation, it shall be possible for the user by visual or other means to confirm that this action has been successfully completed.

   If exposure to light to enable the user to view the product could adversely affect the medicinal product and/or therapy, this shall be addressed in the risk assessment.

b) It shall be determined, by risk assessment, if a residual scale is required and how much of the deliverable volume shall be visible.

c) NISs shall be designed in such a way that if the container is manufacturer-filled, the deliverable volume shall be consistent with the volume that is declared on the label of the container for which they are designed, with the exception of system designations B2 and D2.

d) User-filled NIS reservoirs shall be designed in such a way that they are capable of being filled to and delivering the intended deliverable volume. If the user is provided a pre-measured volume, it shall be ensured that when the volume is transferred in accordance with the instructions for use, the NIS reservoir contains adequate medicinal product to ensure the intended dose is delivered. If the user is provided with a volume greater than a single intended dose, feedback shall be provided to the user that an intended volume has been filled.

   In cases where the volume is provided pre-measured, it is recommended that the NIS indicates that an intended volume has been filled.

   The risk of under- and over-filling should be assessed.

e) NISs where the user is required to set the dose, shall provide indication (by visual and either tactile and/or audible means) of the dose setting action. Once set, the NIS shall provide an indication of the dose that has been set. This information can be displayed in drug-specific units (e.g. millilitres, milligrams, international units) or in a unit of measure (e.g. number, letter, percentage) appropriate for the drug to be delivered.

f) NISs where the manufacturer has set the dose shall indicate the dose on the NIS or the system labelling, as appropriate.

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

h) 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 at least be visible.

i) The NIS shall indicate by visual, audible or tactile means, or any combination of these that the delivery operation (e.g. injection stroke) has been completed. These means should be appropriate to the intended use of the NIS.

j) NISs with system designation B2 or D2 shall be designed in such a way that under normal use conditions, it shall not be possible to deliver the residual volume following actuation.

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k) Variable dose NISs with system designation A or C shall be designed so that they:

   1) do not allow a larger dose to be set than the remaining deliverable volume; or

   2) do not allow dose delivery if the set amount exceeds the remaining deliverable volume; or

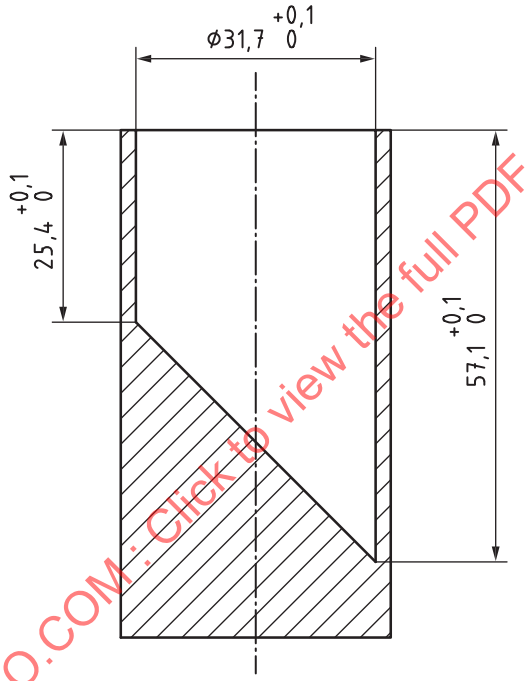
   3) indicate the amount of medicinal product delivered; or

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

l) Fixed multi-dose NISs with system designations A or C shall not allow setting of the dose if the remaining deliverable volume is insufficient for the full fixed dose.

m) If any component intended to be removed from a NIS fits entirely in any orientation into the small part cylinder shown in Figure 3, without compressing the component, then the NIS shall be accompanied by an age warning (see Annex E).

Dimensions in millimetres



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

Figure 3 — Small part cylinder

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n) Under normal conditions of use, the expected exposure to or contact with the medicinal product for which a NIS is specified for shall not adversely affect the primary functions of the NIS (see Annex G).

o) Claims of ingress protection (IPXX) shall be tested in accordance with applicable clauses of IEC 60529. This applies to all NISs with claims of ingress protection, including those without electronics.

p) Biocompatibility of the NIS shall be established in accordance with ISO 10993-1 (see also Annex C).

q) The NIS shall maintain its primary functions after exposure to the conditions under which the finished product will be shipped.

r) When the NIS labelling specifies the use of a specific brand accessory, component or part that is not provided with the NIS, regardless of whether its use is optional or required, it shall be confirmed that the NIS and the accessory perform as intended when used together, and that the combined use

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does not introduce new and unacceptable risks to patient safety. Likewise, separately delivered NIS components shall be tested and demonstrated to be functionally compatible.

s) In the case where the medicinal product requires preparation (e.g. reconstitution or mixing) in the NIS prior to delivery to the patient, the medicinal product exiting the fluid path shall meet its specification (e.g. content uniformity in accordance with applicable pharmacopeial requirements) throughout the delivery.

NOTE 1 Automated medicinal product preparation requirements are covered by ISO 11608-5.

t) The quality of the medicinal product shall meet specifications after transfer to, contact with, storage in, or delivery through the NIS.

NOTE 2 Medicinal product compatibility is addressed in ISO 11608-3.

u) Cleaning processes for the NIS described in the instructions for use, shall be assessed to not adversely impact the primary functions of the NIS.

v) The NIS shall not compromise container or fluid path sterility.

w) When the design of the NIS is such that the user does not have control over the depth to which the needle is inserted, injection depth control shall be considered an automated function.

NOTE 3 Automated functions are addressed in ISO 11608-5.

x) If sharps protection is claimed, the requirements of ISO 23908 shall be fulfilled.

y) Any marking on the NIS that is needed for the safe use of the NIS shall remain visible, and legible when used, stored and cleaned in accordance with the instructions for use.

5.7 Design verification

5.7.1 General

Verification of the design specifications shall be conducted on product representative of final NIS. Verification can be performed through many mechanisms, including testing. The adequacy of the type of verification used shall be justified and documented. When testing is used, such as according to the methods contained, or referenced in this document, the verification (other than for primary functions – see 5.7.2) shall ensure a probability content of 95 % (with 95 % confidence) unless a different probability content is determined to be appropriate by risk assessment. Testing (other than for primary functions – see 5.7.2) shall be conducted without preconditioning, at standard atmosphere, unless the normal use case of the product indicates an alternative test condition.

5.7.2 Primary functions requirements

Primary functions shall be identified through an assessment of the risk associated with each design specification (see Figure 2). At minimum, primary functions shall include the dose delivery function, as specified by the dose accuracy requirements.

Primary functions shall be assessed in accordance with Table 3 conditions and preconditions based on the system designation. The NIS shall maintain its primary functions after being subjected to test methods described in 10.1, 10.2 and 10.3 and in accordance with risk-based acceptance criteria described in 7.4.5.

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

NOTE 1 The identification of primary function can be iterative. The manufacturer might have to revisit the process of identifying the primary functions during the lifecycle of the NIS.

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Even though there might be many potential causes for a NIS failing to perform its primary function, it is recommended to focus on the "top level" characteristics or functions as the primary functions to be assessed in testing. For example, multiple design characteristics combine to ensure an accurate dose is delivered, but only "dose accuracy" needs to be identified as a primary function. Tracing the sub-level characteristics (e.g. fill volume, spring force, component dimensions etc. that can result in inaccurate dosing) that support the top- level primary functions can help in performing root cause analysis of a failure of the NIS to meet the primary functions.

NOTE 2 Maintenance of the integrity of the sterile barrier of the device portion of the NIS, although not a "function", can be assessed after each preconditioning in Table 3, if determined to be appropriate by risk assessment.

NOTE 3 Primary functions selection of the NIS can be affected by what is known about the specific medical condition the product will be indicated for and/or understanding of the properties of the medicinal product. For example, NISs containing medicinal products for the immediate treatment of acute, life-threatening conditions can require a greater selection of primary functions than those for chronic, non-life-threatening conditions.

6 Reagent and apparatus

6.1 General

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

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

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

$$E = \frac{n_{\text{correct}}}{n_{\text{total}}}$$

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

$$P_{\text{FA}} = \frac{n_{\text{FA}}}{n_{\text{reject}}}$$

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

where:

n_{total} is the total number of assessments made

n_{correct} is the number of correct assessments made

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

n_{reject} is the total number of rejectable items

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

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6.2 Test liquid

The test liquid shall be either the medicinal product intended to be injected by the NIS, or a liquid with physical properties that mimic the original medicinal product for the respective test.

6.3 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 and rigidly supported.

7 Assessment of dose accuracy and other primary functions

7.1 General

When testing is used to assess conformance of primary functions, this is performed by selecting and testing a variable number of NISs. The number depends on the container and performance requirements for a given test. For dose accuracy, in the specific instance of user-filled single-dose NISs designed to fully empty the deliverable portion of the container, accuracy can be evaluated as dose-delivery efficiency. In the instance of manufacturer-filled single-dose NISs designed to fully empty the deliverable portion of the container, one-sided accuracy can be evaluated as the minimum deliverable dose.

Assuming that the measurements are normally distributed (or can be transformed to normal) and that all measurements are independent, the following methods enable 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. If the data is not normal or is not able to be transformed to normal, refer to Annex F. The statistical tolerance interval is either two-sided or one-sided and the limits of the interval are called "statistical tolerance limits" or "natural limits of the process".

7.2 Dose accuracy

7.2.1 General

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

The following equation can be used to convert gravimetric measurements to volumetric:

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

The following subclauses describe the sampling requirements for dose accuracy.

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	7.2.3.1	7.2.3.2.1	7.2.3.2.2.	7.2.3.1	7.2.3.2.1	7.2.3.2.2
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

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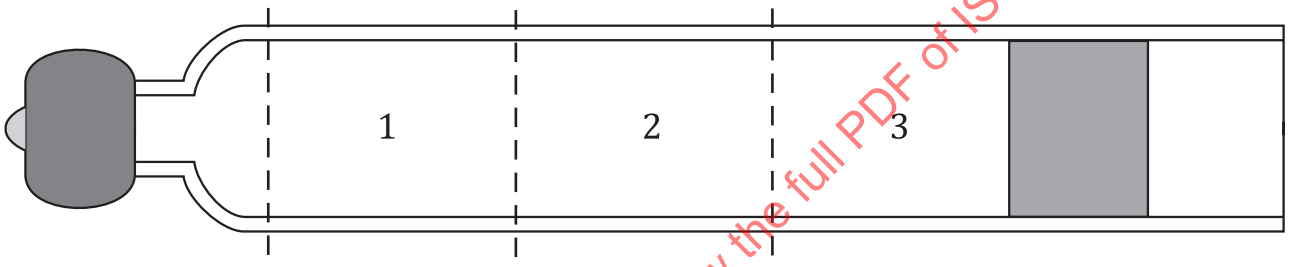
Table 2 *(continued)*

Dose accuracy matrix	System designation					
	A	B1	B2	C	D1	D2
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)	7.4.3	N/A	N/A	7.4.3	N/A	N/A
Calculate dose delivery 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

See Annex F for a detailed discussion of sampling plans for both variable and attribute data.

7.2.2 Dosing regions

For multi-dose containers, the dosing regions are illustrated in Figure 4 (a cartridge is shown as an example). Different container designs require verification that all three regions (full, half-way used and almost empty) perform predictably.



Key

1 front 1/3 (almost empty)
2 middle 1/3 (halfway used)
3 rear 1/3 (full)

NOTE 1 If the sum of the doses set is greater than half the deliverable volume of the container, the container can be divided into two regions.

NOTE 2 If the sum of the doses set is greater than the deliverable volume of the container, the container can be considered one region.

Figure 4 — Schematic showing three dosing regions

7.2.3 Dose settings

7.2.3.1 Multi-dose container (system designations A and C)

7.2.3.1.1 Variable dose NISs

a) To conduct these calculations, pick three dose sizes which will each be called V_{set}. These three values shall be called a minimum (V_{min}), a midpoint (V_{mid}) and a 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.).

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

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

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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}

For a given test, dose accuracy shall be 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).

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.

d) Dosing is designed such that:

— V_{set} is delivered from the front 1/3, middle 1/3 and rear 1/3 regions of the container closure, as shown in Figure 4; or

— is uniformly sampled from regions representing the deliverable volume of the container, as determined in the risk assessment.

7.2.3.1.2 Fixed-dose NISs

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 regions of the container closure, as shown in Figure 4; or

— is uniformly sampled from regions representing the deliverable volume of the container, as determined in the risk assessment.

7.2.3.2 Single-dose containers

7.2.3.2.1 Complete evacuation (system designations B1 and D1)

For system designations B1 and D1, one dose is used; V_{set} is equal to the minimum deliverable dose, unless two-sided limits are used in which case V_{set} is equal to the target dose.

For user-filled system designations B1 and D1, where the instructions for use allow a choice of more than one volume to fill the reservoir, the range of allowable fill volumes should be assessed (e.g. by bracketing minimum and maximum fill volumes), as determined by the risk assessment.

7.2.3.2.2 Partial evacuation (system designations B2 and D2)

7.2.3.2.2.1 Variable dose NISs

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

7.2.3.2.2.2 Fixed dose NISs

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

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7.3 Sampling for other primary functions

The treatment of dose accuracy as variable data can be applied to other primary functions, if identified. In that case, the same techniques can be applied whereby V_{set} is replaced with P_{set}. Subclauses 7.4.1 and 7.4.5 should be reviewed for making variable data assessments in terms of P_{set}.

7.4 Assessment

7.4.1 General

The following focuses on dose accuracy in terms of V_{set}. Subclause 7.4.5 addresses acceptance criteria for all potential primary functions, be they variable or attribute data.

To pass the requirement (for system designations A, C, B2, D2), there shall be a 95 % confidence that at least the probability content, p, of all measurements will fall within the proposed upper and lower specification limits. For dose accuracy, the three dose settings (one dose setting in the case of fixed-dose systems) apply.

To pass the minimum requirement (one-sided) for dose accuracy (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 equal to or above the lower specification limit, which is defined by the minimum deliverable dose specified.

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 equal to or above the proposed 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 dose accuracy requirement for the last dose delivered from the device (for system designations A and C), where the NIS 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 (or other measurement) per NIS shall be used for each V_{set} (P_{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)

Two-sided dose accuracy limits are defined in absolute or relative terms, by applying the following rules, considering the V_{set}, the minimum dialling resolution, R_D, and the transition point, P_T, of the NIS:

— Rule 1: Absolute error, α, expressed in millilitres (ml), is equal to the R_D of a variable dose NIS and is 0,01 ml for a fixed dose NIS. Absolute error is used to define the upper specification limit, U_{SL}, and lower specification limit, L_{SL}, when V_{set} is equal to or below the P_T .

— Rule 2: Relative error, β, is equal to 5 % of V_{set} and is used to calculate the dose accuracy U_{SL} and L_{SL} when V_{set} is above the P_T.

These rules result in the same dose accuracy limits for V_{set}, expressed in ml, when V_{set} is equal to the P_T.

P_T is the volume (expressed in ml) at which the absolute error is equal to 5 % of V_{set} and is calculated using:

$$P_T = (100\% \times \alpha) / 5\%$$

EXAMPLE 1 For R_D equal to 0,01 ml, α is 0,01 ml.

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Therefore:

$$P_T = (100\% \times \alpha) / 5\%$$

EXAMPLE 2 For R_D equal to 0,005 ml, α is 0,005 ml, therefore:

$$P_T = (100\% \times \alpha) / 5\%$$

For fixed-dose NISs, the P_T is defined as 0,2 ml.

Applying rules 1 and 2 above, the upper and lower specification limits are calculated as follows:

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

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

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

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

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

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

For system designations A, C, B2 and D2, if, according to the risk assessment, the intended dose sizes and accuracy requirements are more appropriately specified individually (i.e. rules 1 and 2 are not applied) rather than by absolute or relative ranges, the dose sizes tested, and their specification limits shall be justified and documented. In such cases, the specification limits shall be no greater than the R_D of the needle-based system. For system designations B2 and D2, the dialling resolution requirement does not apply.

Doses lower than the transition point allow for a percentage of dose variation greater than 5 %, which is the standard limit for doses over the transition point. For NISs that enable doses under the transition point, a risk-based assessment shall be provided to justify that this increased allowable dose accuracy range is acceptable for the therapy indicated. This can be a general comparison to currently marketed products for NISs designed or to be indicated for general injection, or a specific justification based on the safety of the medicinal product when the NIS is designed or to be indicated for only one medicinal product. Special attention should be paid for NIS that are designed or to be indicated for concentrated medicinal products (e.g. high concentration insulins).

For system designations A and C, if, according to the 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)

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

For manufacturer-filled containers, the one-sided lower specification limit for the minimum deliverable dose is determined from the risk assessment.

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For NIS that are designed to evacuate the entire container, an assessment shall determine the maximum dose that could possibly be delivered (maximum volume in the container) and evaluate whether it could result in unacceptable harm to the patient. If unacceptable harm is possible, then a maximum dose specification shall be established and a two-sided dose accuracy assessment shall be used, follow 7.4.2.1.

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

Fixed dose NISs are excluded from this requirement.

For variable-dose NISs that do not allow the setting of a dose greater than the remaining deliverable volume, dose accuracy limits shall be established as described in 7.4.2 using either V_{set} equal to V_{min} or the P_T dose. It shall be determined which to use based on the risk assessment.

For variable-dose NISs that allow the setting of a dose greater than the remaining deliverable volume, the last dose is evaluated in terms of dose error since normal variation in system dimensions makes it impossible to set the exact same last dose from one NIS 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 1,0 × P_T and 1,4 × P_T, so that a mean dose error (ideally centred on zero) is calculated for each of the doses. For rationale, see A3.2.2.

Individual last-dose errors (expressed as a percentage) can be calculated as shown in the following example using a P_T of 0,20 ml:

a) The range of doses that can be used to determine last-dose accuracy would be from 0,20 ml to 0,28 ml for this example, where the P_T is 0,20 ml. This range is ± 0,20 × P_T, centred at 1,20 P_T. 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:

$$\varepsilon_{meas} = \frac{V_{meas} - V_{ind}}{V_{ind}} \times 100$$

where:

ε_{meas} is the relative error on the last dose expressed in per cent, and

V_{ind} is the dose volume indicated (where the manner of indication depends on the design implementation of 5,6 k))

c) The upper specification limit, P_{USL}, for the mean last-dose error (i.e. relative error):

P_{USL} = 5,0 %

d) The lower specification limit, P_{LSL}, for the mean last-dose error (i.e. relative error):

P_{LSL} = -5,0 %

e) Conformity is assessed in accordance with 7.4.5.1 using ε_{meas}.

If, according to the risk assessment, a different last-dose measurement range is used [e.g. (1,3 ± 0,3) × P_T], the specification limits for last-dose error shall be stated in the instructions for use.

If a variable-dose NIS allows the setting of a dose greater than the remaining volume, the last dose accuracy is evaluated for the target dose V_{set} = 1,20 × P_T. However, as it is impossible in these NISs to reach the targeted dose exactly, a deviation of 0,20 × P_T from that target dose is accepted.

NOTE For further explanation of last-dose accuracy, see A.3.2.2.

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

Calculate dose efficiency as a percentage by:

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

where:

m_1 is mass of device and container as received by the user (i.e. empty);

m_2 is mass of device and container as filled;

m_3 is mass of device and container and any residual volume after delivery.

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

7.4.5 Acceptance criteria

7.4.5.1 Variable data

A NIS population satisfies the requirements for accuracy (or other variable data) when, for a given V_{set} or P_{set}, the following are fulfilled:

Two-sided:

$\bar{x} - (k \times s) \geq P_{LSL}$ and

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

One-sided:

$\bar{x} - (k \times s) \geq P_{LSL}$ or

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

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. For normally-distributed data, this can be taken from the tables in Annex B.

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 16269-6:2014, Annex E, lists the sample sizes for the construction of two-sided statistical tolerance intervals when the true population mean and standard deviation are not known.

Table B.1 provides one-sided tolerance limits for the 95 % confidence level for both the 95 % and 97,5 % probability contents, p, and Table B.2 contains more comprehensive two-sided tolerance limits for the 95 % confidence level.

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7.4.5.2 Attribute data

A NIS population satisfies the requirements when, for a given V_{set} or P_{set}, the following are fulfilled:

— clear acceptance criteria are defined for the individual sample;

— using the appropriate probability content, p, from the test case matrix (Table 3);

— using a confidence level of 95 %;

— statistical analysis demonstrates that, with the stated confidence level, at least a proportion, p, of the population meets the acceptance criteria. For the recommended zero-defect acceptance plan, this is fulfilled when a number of individual samples corresponding at least to the recommended sample size (see Table 3) have been tested, and all have passed.

NOTE See Annex F for rationale for sampling.

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.

9 Test case matrix

Table 3 summarizes test requirements for the system designations described in 5.2. The testing procedures, including preconditioning and in-use requirements, are described in Clause 10.

Annex A provides the rationale for the required tests. Risk management for the NIS may provide for additional testing above the minimum requirements presented in Table 3. The following shall be applied in reading the matrix:

a) for all test cases, the confidence level shall be 95 %;

b) for all dose accuracy tests except for last dose accuracy, the number of replicates for each NIS shall be 1. For variable-dose NIS, one test replicate includes measuring V_{min}, V_{mid} and V_{max};

c) for each V_{set} or P_{set}, the target k corresponds to the number of measurements per V_{set} or P_{set}, n. If the total number of measurements is changed, the corresponding target k shall be changed as well;

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

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

f) the number of NISs, Y, (and containers for system designations A and C) shall be calculated prior to testing such that the number of measurements (n) provided in Table 3 are obtained. Only one dose (or other measurement) per NIS can be used for each V_{set} (P_{set}) for a given test.

g) sample sizes are suggested; however, other sample sizes can be chosen. However, if smaller than 20 samples, it shall be justified that the sample size is representative of the design.

NOTE See Annex F for additional insight into sample size selection.

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Table 3 — Test case matrix

Test case (with reference to sub-clauses)	System designation				Probability content	Recommendations for variable data (normal distribution or transformed)			Recommendations for attribute data
	A	B	C	D		Number of measurements (n) [a]	Two-sided target k	One-sided target k	Number of measurements (n) [a]
Cool, standard and warm (10.2.1)	X	X	X	X	97,5 %	30 [b]	2,921	2,608	120[b]
Last-dose accuracy (10.2.2)	X	N/A	X	N/A	97,5 %	30	2,921	2,608	120
Life-cycle (10.2.3)	X	X	N/A	N/A	95 %	20	2,760	2,396	60
Free-fall (10.3.1 a and b)	X	X	N/A	N/A	95 %	20	2,760	2,396	60
Free-fall (10.3.1 c and d)	N/A	N/A	X	X	95 %	30	2,555	2,220	60
Dry-heat (10.3.2)	X	X	X	X	97,5 %	30	2,921	2,608	120
Cold-storage (10.3.3)	X	X	X	X	97,5 %	30	2,921	2,608	120
Damp-heat (10.3.4)	X	X	N/A	N/A	95 %	20	2,760	2,396	60
Cyclical (10.3.5)	X	X	N/A	N/A	95 %	20	2,760	2,396	60
Vibration (10.3.6)	X	X	X	X	95 %	20	2,760	2,396	60
Transport (10.3.7)	X	X	X	X	95 %	20	2,760	2,396	60
Functional stability (10.3.8)	X	X	X	X	95 %	20	2,760	2,396	60
Fluid leakage (10.3.9)	X	X	N/A	N/A	95 %	20	2,760	2,396	60

[a] Each test case can have more than one characteristic (e.g. dose accuracy plus others) that needs to be tested. The sample size here is for each characteristic to be tested, although multiple characteristics can be tested on the same set of samples, and potentially at the same time.

[b] For system designation C and D, the sample size is per condition (i.e. cool, standard, warm).

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10 Testing procedures

10.1 General

For each test case described in Clause 10, perform the following evaluations after each preconditioning or in-use test requirement. Unless otherwise instructed for a given test description, perform the evaluation at standard atmosphere conditions in accordance with 10.2.1.1. The order of the evaluations, a) through b) as applicable, is unspecified.

a) Assess primary functions of the NIS in accordance with 5.7.2 and 7. The NIS shall maintain its primary functions after being subjected to preconditioning or in-use requirements described in Clause 10. For the last-dose accuracy test described in 10.2.2, only dose accuracy is required.

b) Perform inspection of every NIS tested in accordance with Clause 11.

For NISs that may operate for extended durations, it shall be considered simulating additional conditions to which the NIS would be subjected as worn before and/or during delivery in addition to the conditioning specified as "normal/anticipated conditions" when testing primary functions.

NOTE See Annex A for test conditions.

10.2 Normal/anticipated condition test cases

10.2.1 Cool, standard and warm atmosphere in-use testing

10.2.1.1 Atmosphere conditions

The assembled NIS with the filled container but without needle (if removable) is placed in a test chamber to precondition for at least 4 h in the atmospheres given in Table 4.

Table 4 — Atmosphere conditions

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

10.2.1.2 In-use testing

For system designations A and B, use the same set of systems at each of the conditions specified in Table 4.

For system designations C and D, use three different sets of systems, one for each of the conditions specified in Table 4.

Test execution shall ensure the NIS is acclimatized to the atmospheric conditions specified in Table 4 during testing. This may be achieved by testing at these atmospheric conditions or by testing at standard atmosphere without time for acclimatization after removal from the test chamber. Testing at standard atmosphere shall be supported by a rationale, and the time from removing the NIS until the end of the test shall be as short as possible.

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

10.2.2.1 General

Last-dose accuracy testing only applies to variable-dose NISs. Fixed-dose NISs shall be excluded from this requirement, as the assessment of last-dose accuracy is included as part of the general dose accuracy requirement, which shall include a representative sample of these last doses.

10.2.2.2 NIS preparation

Select the same NISs previously used for determining dose accuracy in accordance with 10.2.1. For system designation C, new NISs are allowed.

For variable-dose NISs that do not allow the setting of a dose greater than the remaining volume, operate each NIS until a dose, V_{set}, equal to either the V_{min} or transition point, P_T, dose remains. It shall be determined which to use, based on the risk assessment.

For variable-dose NISs that do allow the setting of a dose greater than the remaining volume, operate each NIS until the remaining deliverable volume is between 1,0 x P_T and 1,4 x P_T.

10.2.3 Life-cycle testing (systems designations A and B only) — Preconditioning

The same systems as used in 10.2.1 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 NIS (e.g. cap and needle removal and attachment, injection). The NISs 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.

NOTE Reusable NISs are considered to have two separate mechanisms that can cause failure to meet primary functions. One is due to mechanical or electronic degradation during use and the other is time related, degradation during storage. The impact of mechanical or electronic degradation over use is verified through life-cycle testing (see 10.2.3) and the impact of storage over time is verified through functional stability testing (accelerated or real time, see 10.3.8). These are performed as separate design verification tests and are not intended to be combined.

10.3 Stressed/challenge condition test cases

10.3.1 Free fall testing – Preconditioning

The following list describes free-fall testing of NISs in both vertical and horizontal orientations. Additional and/or different orientations might be required to address worst case depending on risk assessment and the geometry of the NIS.

The sample sizes suggested below assume normality of the subsequent assessment of primary functions (see 10.1 a)). If the data cannot be transformed to normal, different sample sizes will be required.

The quantities of NISs stated for free-fall pre-conditioning are based upon the recommendations for variable data stated in Table 3. Where testing generates attribute data, the quantities for pre-conditioning by free-fall should be increased proportionally to provide the total number of samples required for testing. Exclusions or replacements for container breakages allowed in 10.3.1 may also be increased by up to the same ratio as the increase in total sample size.

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Prepare the NIS according to the instructions for use, including removing from packaging, and - with a new container (where applicable) - proceed as follows:

a) For multidose NIS with replaceable containers (system designation A):

   1) remove any protective cover (e.g. a NIS cap), insert the container, prepare the system for injection (e.g. attach a needle and prime or purge the system);

   2) if possible, replace the protective cover (e.g. for a NIS with a removable needle), take it off and put on the NIS cap;

   3) drop 20 NISs three times by free-fall from a height of (1 000 -0/+100) mm onto the test surface (see 6.3), 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 in a manner obvious to the user, replace the container and continue until all three drops have been performed. The maximum number of replacements for each test orientation shall be three.

b) For multidose NIS with non-replaceable containers (system designation C):

   1) remove any protective cover (e.g. a NIS cap), prepare the system for injection (e.g. attach a needle and prime or purge the system);

   2) prepare the system for injection (e.g. for a NIS with a removable needle), take it off and put on the NIS cap;

   3) drop the NIS by free-fall from a height of (1 000 -0/+100) mm onto the test surface (see 6.3) in accordance with i), ii) and iii), as follows:

      i. horizontal — drop 10 new NISs, taking care to release the NISs in a non-turbulent way;

      ii. vertical A — drop 10 additional new NISs, taking care to release the NISs in a non-turbulent way;

      iii. vertical B — [180° from orientation ii)] drop 10 additional new NISs, taking care to release the NISs in a non-turbulent way.

   4) if a container breaks so that it is completely fractured in a manner obvious to the user, replace the NIS, drop the replacement NIS in the same orientation, and continue until 10 NISs have been dropped without replacement in each orientation. The maximum number of replacements for each orientation shall be four.

   5) all orientations shall be combined for assessment of primary functions [10.1 a)].

c) For single dose NIS with replaceable containers (system designations B1 and B2):

   1) assemble the NIS or insert the primary container closure into the NIS (e.g. place syringe in the reusable auto-injector, insert cartridge in reusable pen or OBDS), but stop before the drug container sterility is broken [e.g. rigid needle shield (RNS) or tip cap is removed, or primary container is breached];

   2) drop 20 NISs three times by free-fall from a height of (1 000 -0/+100) mm onto the test surface (see 6.3), 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;

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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 maximum number of replacements for each test orientation shall be three.

d) For single dose NIS with non-replaceable container (system designations D1 and D2):

1) for prefilled NIS (e.g. prefilled auto-injectors, prefilled pens or prefilled OBDS), stop before the drug container sterility is broken (e.g. RNS or tip cap is removed, or primary container is breached). For user-filled NIS (e.g. unfilled OBDS with reservoir), stop after the reservoir is filled, but before the NIS is placed on the body and/or the fluid flow is activated;

2) if a removable needle has been attached in item 1 above, remove it;

3) drop the NIS by free-fall from a height of (1 000 -0/+100) mm onto the test surface (see 6.3) in accordance with i), ii) and iii), as follows:

i. horizontal — drop 10 new NISs, taking care to release the NISs in a non-turbulent way;

ii. vertical A — drop 10 additional new NISs, taking care to release the NISs in a non-turbulent way;

iii. vertical B — [180° from orientation ii)] drop 10 additional new NISs, taking care to release the NISs in a non-turbulent way.

4) if a container breaks so that it is completely fractured in a manner obvious to the user, replace the NIS, drop the replacement NIS in the same orientation, and continue until 10 NISs have been dropped without replacement in each orientation. The maximum number of replacements for each orientation shall be four;

5) all orientations shall be combined for assessment of primary functions [10.1 a)].

10.3.2 Dry-heat storage – Preconditioning

Precondition the NISs as follows:

a) System designation A and B or C and D (user-filled):

Place unused NISs without containers or needles in a test chamber for at least 96 h in the atmosphere given in Table 5.

Table 5 — Dry-heat temperatures

Condition	Dry heat
Temperature °C	(70 ± 2)
Humidity %RH	(50 ± 10)

b) System designation C and D (manufacturer-filled):

Place unused NISs in a test chamber for at least 96 h at the acceptable high storage temperature, which shall be stated in the instructions for use.

NOTE See A.3.2.2 for details.

10.3.3 Cold-storage - Preconditioning

Precondition the NISs as follows:

a) System designations A and B or C and D (user-filled):

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Place unused NISs without containers or needles in a test chamber for at least 96 h in the atmosphere given in Table 6.

Table 6 — Cold-storage temperatures

Condition	Cold storage
Temperature °C	(−40 ± 3)
Humidity %RH	No humidity requirement

b) System designation C and D (manufacturer-filled):

Place unused NISs in a test chamber for at least 96 h at the acceptable low storage temperature, which shall be stated in the instructions for use.

NOTE See A.3.2.2 for details.

10.3.4 Damp-heat testing (system designations A and B only) — Preconditioning

Precondition the NISs as follows:

Place unused assembled NISs without the containers or needles in a test chamber for at least 96 h in the atmosphere given in Table 7.

Table 7 — Damp heat conditions

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

10.3.5 Cyclical testing (system designations A and B only) — Preconditioning

Precondition the NIS, with the container and without the needle, in accordance with variant 1 [see IEC 60068-2-30:2005, Figure 2 a)] modified as follows:

a) lower temperature of (5 ± 3) °C (no humidity requirement);

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

c) 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.

10.3.6 Vibration testing — Preconditioning

Vibrate the NIS with its container and needle in each of the three axes in accordance with Table 8 and IEC 60068-2-6:2007, Figure 1.

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Table 8 — 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	2 *g*	4
[a] Sweep speed = 1 octave per minute.		

If, according to risk assessment, the NIS is intended to be exposed to vibration during use (e.g. which may be the case for an on-body delivery system, in accordance with ISO 11608-6), then an additional vibration test shall be conducted with a new set of NISs to confirm the product performs its primary function while operating during vibration (vibrated while delivering).

10.3.7 Transport – Preconditioning

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

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

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

NOTE See A.3.3.6.

10.3.8 Functional stability – Preconditioning

Subject a new set of NISs to the labelled storage condition for a time equivalent to the expected service life or labelled expiration date.

NOTE 1 Reusable NISs are considered to be prone to two separate mechanisms that could cause failure to meet primary functions. One is due to mechanical or electronic degradation during use and the other is time related, degradation during storage. The impact of mechanical or electronic degradation over use is verified through life-cycle testing (see 10.2.3) and the impact of storage over time is verified through functional stability testing (accelerated and real time, see Annex D). These are performed as separate design verification tests and are not intended to be combined.

NOTE 2 See Annex D for details.

10.3.9 Fluid leakage (system designations A and B only) - Preconditioning

NOTE The purpose of this test is to evaluate the influence of liquid that leaks from the NIS for example, but not limited to, a broken container, into the NIS.

Precondition the NIS as follows:

a) Remove any removable container holder and pour the contents of one container of the medicinal product into the NIS at the most likely point of entry.

b) Using appropriate safety equipment, shake the NIS in all directions by hand for 30 s.

c) Allow the medicinal product to drain from the original point of fluid entry, for 10 min.

d) Attach a new container.

e) Store the NIS in a horizontal orientation in accordance with the instructions for use, for 24 h.

f) Expel all medicinal product from the container by injections and operate the NIS in accordance with the instructions for use.

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g) Replace the used container with a new one.

h) Store the NIS in a horizontal orientation in accordance with the instructions for use, for 96 h.

i) Expel all medicinal product from the container by injections and operate the NIS in accordance with the instructions for use.

An error that is obvious to the lay user shall be allowed if it does not influence any safety aspects in accordance with a risk assessment as defined in 5.3.

11 Inspection

11.1 General

While there are no specific statistical requirements (i.e. *p*-content and confidence level) for the inspections described in Clause 11, these inspections shall result in zero failures as a consequence of the tests outlined in Table 3 and Clause 10.

11.2 Legibility of markings

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

NOTE 1 The legibility of markings inspection is supposed to ensure that NIS users are able to read the markings under real-life conditions (e.g. limited light intensity) whereas the inspection for defects (11.3) is intended to detect defects during design verification.

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

11.3 Freedom from defects

Visually inspect the NIS for defects using normal or corrected-to-normal vision and environmental lighting conditions of ≥750 lx, and from one reading distance of between 30 cm and 70 cm. In particular, include checking for defects such as:

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

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

c) for NISs with replaceable batteries, the battery compartment failing to remain closed;

d) except for free fall (see 10.3.1), cracked containers or loss of contents in such a way that is obvious to the user.

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

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12 Information supplied with the NIS

12.1 General

The NIS shall be accompanied by information, including instruction for use and markings on user packaging, that is sufficient for its safe use, considering the training and knowledge of intended users and the intended use environment. The information required shall be determined through risk assessment and validated or justified as adequate for safe use using a usability engineering process (see 5.4).

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

NOTE Annex E includes guidance for instructions for use and markings.

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Annex A
(informative)

Testing rationale

A.1 Uncertainty of measurement (see 5.5)

The requirements in 5.5 to evaluate and express the uncertainty of measurement apply to measurements of physical characteristics of the NIS such as the performance of primary functions, geometrical specifications, etc.

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

The manufacturer is expected to assess the impact of any variations of the strength or quality of test conditions and preconditions on the subsequent measurements of the physical characteristics of the product and include this in the evaluation of the uncertainty of that measurement.

A.2 Apparatus (see 6.1)

The requirement of 6.1 for the suitability of test systems used for the measurement of primary functions are intended to apply to the test system when used in accordance with the applicable test method.

A risk-based approach is expected to be used for establishing appropriate requirements for the accuracy of the test system, while the requirements for the precision are given in 6.1.

For gravimetric measurements of dose accuracy, a resolution of 1 % or smaller of the mass of the minimum dose delivered (minimum V_{set}) is recommended.

Where a new test method needs to be developed and validated, the validation is expected to follow industry practice. Guidance for this purpose can for instance be found in ISO/IEC 17025.

A.3 Testing requirements (see Clause 10)

A.3.1 General test requirements (see 10.1)

The required stressed/challenge preconditioning of samples specified in this document, prior to the primary function testing, subjects the test samples to conditions/stresses at the extremes of foreseeable use or exposure. As such these conditions constitute an upper (or lower) bound on the imaginable variation of the stress factors. It is not required to combine two or more types of preconditioning before testing the samples unless, as identified by risk assessment, there is a high probability that the product will be exposed to them during normal use. This also does not prevent a manufacturer from, at their discretion, subjecting the samples to multiple preconditioning before testing in order to reduce the required number of test samples.

A.3.2 Normal/anticipated conditions

A.3.2.1 Standard, cool and warm atmosphere in-use testing (see 10.2.1)

These tests are intended to measure the performance of the NIS 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

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and indoor conditions encompass the year-round variations in "room temperature". This document expects that the manufacturer would not change the test conditions without a risk-based justification based on the expected "in-use" conditions (as defined in the labelling).

A.3.2.2 Last-dose accuracy testing (see 10.2.2)

The last dose is considered as important as any other dose and should therefore meet the same accuracy requirements, unless risk assessment determines otherwise. However, based on NIS design, testing last-dose accuracy can be problematic and might require different methods, particularly for NISs 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.

In this document, the procedure is updated for testing last-dose accuracy for NISs that permit setting of doses greater than the remaining volume. The range of remaining volumes usable for last-dose accuracy testing has been changed to now be (1,0 – 1,4) × P_T. This has been done to simplify the calculations of the tolerance range and to allow for a greater range of remaining volumes to be usable when testing.

A.3.2.3 Life-cycle testing (see 10.2.3)

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.3.3 Stressed/challenged conditions

A.3.3.1 Free-fall testing (see 10.3.1)

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 NISs are tested in a condition consistent with that in which they would be taken from their place of storage in preparation for use. NISs are tested with the container installed, without a needle (if removable) and with a cap (if provided). Multi-dose NISs are primed (with removal of the needle and replacement of the cap) as representing its most common ready-to-use condition. Single-dose NISs 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, as this is a height at which the NIS would likely be placed by the user in preparation for use (e.g. on a tabletop).

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 NIS.

The free fall test accommodates the replacement of a protective cap, which can occur when the NIS is used at a later time.

Figure A.1 illustrates the free fall testing plan for the various NIS system designations.

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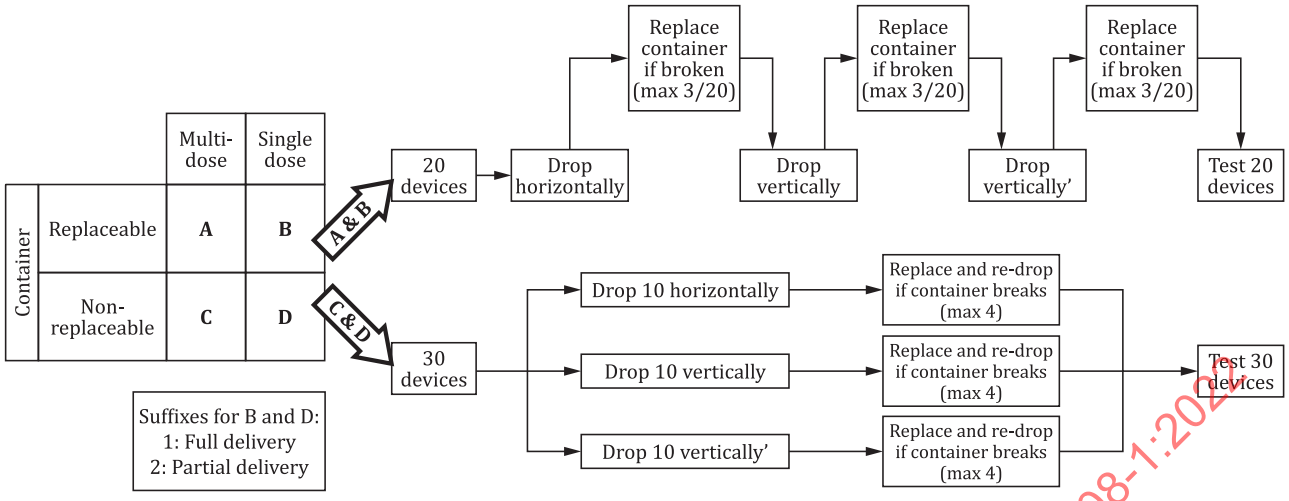

NOTE "vertically" and "vertically'" (with apostrophe) represent the two vertical orientations described in 10.3.1.

Figure A.1 — Free fall testing for various NIS system designations

The allowable replacements differ between system designations, for the following reasons:

— For NISs with system designations A and B (with replaceable containers), 3 out of 20 containers are accepted to be broken in each direction (15 %). These systems are tested from multiple orientations.

— For NISs with system designations C and D (with non-replaceable containers), 4 out of 14 containers are accepted to be broken in each direction (28,6 %). These systems are tested from only one direction due to their limited in-use life.

The previous edition of this document (2014) allowed a maximum of 3 out of 10 NISs to be replaced, or 30 %. A sample size of 7 NISs from each orientation was, however, seen as inadequate for ensuring representative sampling since it did not include language that required the NISs in which the 3 were replaced to be re-tested. Language has been included to ensure that free fall preconditioning was conducted on the replaced samples. To retain equivalent requirements for both the containers themselves and the NIS protecting the container during free fall, the number of allowed replacements has been raised from 3 to 4, making it, worst-case, 4 out of 14, or 28,6 %.

While it is understood that the NIS 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 (system designations A and B) or four failures (system designations C and D), the test is considered to have failed. Additionally, instances where the container damage is not evident to the user (e.g. micro-cracks jeopardizing medicinal product sterility or secondary liquid paths) are considered to have failed as a function of the visual and functional investigation. All other failures of the NIS to meet the primary functions are considered failures.

A.3.3.2 Dry-heat and cold-storage testing (see 10.3.2 and 10.3.3)

These tests are intended to measure the performance of the NIS after exposure to extreme hot and cold storage and shipping conditions as well as potential extreme user interactions (e.g. placing the NIS on a car dashboard in hot weather or accidentally storing the NIS 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 medicinal product is supplied manufacturer-filled, or in the same package as the injection NIS, and when the medicinal product requires controlled shipping and storage conditions to ensure potency and stability. Similarly, modifications to the test conditions

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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 NIS performance. It can also be helpful in assessing potential excursions from controlled storage and shipping conditions across the supply chain.

A.3.3.3 Damp-heat testing (see 10.3.4)

This test is intended to measure the performance of the NIS after exposure to the same dry-heat test temperature, but at much higher humidity. 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 NIS 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 NIS 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.3.3.4 Cyclical atmosphere testing (see 10.3.5)

This test is intended to apply stress to the NIS design. The test conditions 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 NIS components. While the formation of condensation is of particular interest for electronic NISs, 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 NISs.

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 NIS 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.3.3.5 Vibration testing (see 10.3.6)

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

A.3.3.6 Transport testing (see 10.3.7)

Transport testing is intended to simulate the shipping of the product from the point of manufacture to the point where the product is handled by the user. For that reason, this test is carried out on the NIS in its final packaging as it is intended to be shipped.

As shipping conditions can vary greatly, a worst-case approach is often used when designing transport tests to ensure that NIS in its final packaging can meet its requirements after all applicable shipping conditions.

Sufficient NISs are subjected to transport testing to enable testing of primary functions. The sample sizes recommended in Table 3 pertain to the subsequent testing of primary functions and does not apply to the number of NISs to be subjected to transport testing.

A variety of other standards (such as ASTM D4169 and ISTA 3A) exist for the design of transport studies. This document does not require a specific approach to be taken to the design of the transport studies.

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A.3.3.7 Functional stability testing (see 10.3.8)

Functional stability testing is intended to demonstrate that the NIS meets its primary functional requirements at the end of its expected service life or labelled expiry date. Usage at the very end of the useful life is, in and of itself, considered the worst-case situation, and it is therefore categorized as a stressed/challenge condition test case (see Annex D).

A.3.3.8 Fluid leakage testing (see 10.3.9)

Fluid leakage testing is intended to simulate the use of a NIS of system designation A or B where the container has previously fractured, to assess the extent to which such leakage of the medicinal product into the mechanism of the NIS might hinder its performance.

This test is not required for system designations C and D as a completely broken cartridge, such as is simulated by this test, will force the user of these system designations to take a new NIS into use.

A.4 Freedom from defects (see 11.3)

This inspection is intended to detect any defects which can have occurred to the NIS which can impact the safe use or the primary functions of the NIS.

As the list of defects provided in 11.3 is not exhaustive, the manufacturer should use a risk-based approach to assess what defects may impact safely or adversely impact the performance of primary functions.

The inspection is intended to be carried out in good, laboratory lighting conditions.

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Annex B
(normative)

One- and two-sided tolerance limit factors, *k* (for normally distributed data)

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

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

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	6,612	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

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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

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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

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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

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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
225	0,801	1,439	1,825	2,162	2,555	3,376	4,055
230	0,800	1,437	1,823	2,160	2,552	3,373	4,051
235	0,798	1,436	1,821	2,157	2,549	3,370	4,047
240	0,797	1,434	1,819	2,155	2,547	3,367	4,043
245	0,796	1,432	1,817	2,153	2,544	3,363	4,040
250	0,795	1,431	1,815	2,151	2,542	3,361	4,036
255	0,793	1,429	1,814	2,149	2,540	3,358	4,033
260	0,792	1,428	1,812	2,147	2,537	3,355	4,029
265	0,791	1,426	1,810	2,145	2,535	3,352	4,026
270	0,790	1,425	1,809	2,143	2,533	3,349	4,023
275	0,789	1,423	1,807	2,141	2,531	3,347	4,020
280	0,788	1,422	1,805	2,140	2,529	3,344	4,017
285	0,787	1,421	1,804	2,138	2,527	3,342	4,014
290	0,786	1,419	1,802	2,136	2,525	3,340	4,012
295	0,785	1,418	1,801	2,135	2,524	3,337	4,009
300	0,784	1,417	1,800	2,133	2,522	3,335	4,006
310	0,782	1,415	1,797	2,130	2,518	3,331	4,001
320	0,780	1,412	1,794	2,127	2,515	3,327	3,996
330	0,778	1,410	1,792	2,124	2,512	3,323	3,992
340	0,777	1,408	1,790	2,122	2,509	3,319	3,988
350	0,775	1,406	1,787	2,119	2,506	3,316	3,983
360	0,774	1,404	1,785	2,117	2,504	3,312	3,980
370	0,772	1,403	1,783	2,115	2,501	3,309	3,976
380	0,771	1,401	1,781	2,113	2,499	3,306	3,972
390	0,770	1,399	1,780	2,111	2,496	3,303	3,969
400	0,769	1,398	1,778	2,109	2,494	3,300	3,965
425	0,765	1,394	1,774	2,104	2,489	3,294	3,957
450	0,763	1,391	1,770	2,100	2,484	3,288	3,950
475	0,761	1,388	1,766	2,096	2,480	3,282	3,944
500	0,758	1,385	1,763	2,092	2,475	3,277	3,938
525	0,756	1,382	1,760	2,089	2,472	3,272	3,932
550	0,754	1,380	1,757	2,086	2,468	3,268	3,927
575	0,752	1,378	1,755	2,083	2,465	3,264	3,922
600	0,751	1,376	1,752	2,080	2,462	3,260	3,918
625	0,749	1,374	1,750	2,077	2,459	3,256	3,913
650	0,748	1,372	1,748	2,075	2,456	3,253	3,910
700	0,745	1,368	1,744	2,071	2,451	3,247	3,902
750	0,743	1,365	1,741	2,067	2,447	3,241	3,896
800	0,740	1,363	1,737	2,063	2,443	3,236	3,890
850	0,738	1,360	1,734	2,060	2,439	3,232	3,885

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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
900	0,736	1,358	1,732	2,057	2,436	3,227	3,880
950	0,735	1,356	1,729	2,054	2,433	3,224	3,875
1 000	0,733	1,354	1,727	2,052	2,430	3,220	3,871
1 500	0,722	1,340	1,712	2,035	2,411	3,195	3,842
2 000	0,716	1,332	1,703	2,024	2,399	3,181	3,825
3 000	0,708	1,323	1,692	2,012	2,385	3,164	3,805
5 000	0,700	1,313	1,681	2,000	2,372	3,147	3,786
10 000	0,693	1,304	1,670	1,988	2,358	3,130	3,766
∞	0,674	1,282	1,645	1,960	2,326	3,090	3,719

Table B.2 — Two-sided tolerance limit factors

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

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Table B.2 *(continued)*

Confidence = 95 %							
n	*p* = 0,750	*p* = 0,900	*p* = 0,950	*p* = 0,975	*p* = 0,990	*p* = 0,995	*p* = 0,999
26	1,539	2,199	2,619	2,993	3,437	3,744	4,385
27	1,529	2,184	2,601	2,973	3,415	3,720	4,356
28	1,519	2,170	2,585	2,954	3,393	3,696	4,330
29	1,510	2,157	2,569	2,937	3,373	3,675	4,304
30	1,501	2,145	2,555	2,921	3,355	3,654	4,281
31	1,493	2,134	2,541	2,905	3,337	3,635	4,259
32	1,486	2,123	2,529	2,891	3,320	3,617	4,238
33	1,478	2,113	2,517	2,877	3,305	3,600	4,218
34	1,472	2,103	2,505	2,864	3,290	3,584	4,199
35	1,465	2,094	2,495	2,852	3,276	3,569	4,182
36	1,459	2,086	2,484	2,840	3,263	3,555	4,165
37	1,454	2,077	2,475	2,829	3,250	3,541	4,149
38	1,448	2,070	2,466	2,819	3,238	3,528	4,134
39	1,443	2,062	2,457	2,809	3,227	3,516	4,119
40	1,438	2,055	2,448	2,799	3,216	3,504	4,105
41	1,433	2,049	2,440	2,790	3,205	3,492	4,092
42	1,429	2,042	2,433	2,781	3,196	3,482	4,080
43	1,424	2,036	2,425	2,773	3,186	3,471	4,068
44	1,420	2,030	2,418	2,765	3,177	3,461	4,056
45	1,416	2,024	2,412	2,757	3,168	3,452	4,045
46	1,412	2,019	2,405	2,750	3,160	3,443	4,034
47	1,409	2,014	2,399	2,743	3,151	3,434	4,024
48	1,405	2,009	2,393	2,736	3,144	3,425	4,014
49	1,402	2,004	2,387	2,729	3,136	3,417	4,004
50	1,398	1,999	2,382	2,723	3,129	3,409	3,995
51	1,395	1,994	2,376	2,717	3,122	3,401	3,986
52	1,392	1,990	2,371	2,711	3,115	3,394	3,978
53	1,389	1,986	2,366	2,705	3,108	3,387	3,969
54	1,386	1,982	2,361	2,700	3,102	3,380	3,961
55	1,383	1,978	2,356	2,694	3,096	3,373	3,953
56	1,381	1,974	2,352	2,689	3,090	3,367	3,946
57	1,378	1,970	2,347	2,684	3,084	3,361	3,939
58	1,376	1,967	2,343	2,679	3,079	3,355	3,932
59	1,373	1,963	2,339	2,675	3,073	3,349	3,925
60	1,371	1,960	2,335	2,670	3,068	3,343	3,918
61	1,369	1,957	2,331	2,666	3,063	3,338	3,912
62	1,366	1,953	2,327	2,661	3,058	3,332	3,905
63	1,364	1,950	2,324	2,657	3,053	3,327	3,899
64	1,362	1,947	2,320	2,653	3,048	3,322	3,893

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Table B.2 *(continued)*

Confidence = 95 %							
n	*p* = 0,750	*p* = 0,900	*p* = 0,950	*p* = 0,975	*p* = 0,990	*p* = 0,995	*p* = 0,999
65	1,360	1,944	2,317	2,649	3,044	3,317	3,887
66	1,358	1,941	2,313	2,645	3,039	3,312	3,882
67	1,356	1,939	2,310	2,641	3,035	3,307	3,876
68	1,354	1,936	2,307	2,638	3,031	3,303	3,871
69	1,352	1,933	2,304	2,634	3,027	3,298	3,866
70	1,350	1,931	2,300	2,631	3,023	3,294	3,861
71	1,349	1,928	2,297	2,627	3,019	3,290	3,856
72	1,347	1,926	2,295	2,624	3,015	3,285	3,851
73	1,345	1,923	2,292	2,621	3,011	3,281	3,846
74	1,344	1,921	2,289	2,617	3,008	3,277	3,841
75	1,342	1,919	2,286	2,614	3,004	3,274	3,837
76	1,341	1,917	2,284	2,611	3,001	3,270	3,832
77	1,339	1,914	2,281	2,608	2,997	3,266	3,828
78	1,337	1,912	2,278	2,605	2,994	3,262	3,824
79	1,336	1,910	2,276	2,603	2,991	3,259	3,820
80	1,335	1,908	2,274	2,600	2,988	3,255	3,816
81	1,333	1,906	2,271	2,597	2,984	3,252	3,812
82	1,332	1,904	2,269	2,594	2,981	3,249	3,808
83	1,330	1,902	2,267	2,592	2,978	3,246	3,804
84	1,329	1,900	2,264	2,589	2,975	3,242	3,800
85	1,328	1,899	2,262	2,587	2,973	3,239	3,797
86	1,327	1,897	2,260	2,584	2,970	3,236	3,793
87	1,325	1,895	2,258	2,582	2,967	3,233	3,790
88	1,324	1,893	2,256	2,580	2,964	3,230	3,786
89	1,323	1,892	2,254	2,577	2,962	3,227	3,783
90	1,322	1,890	2,252	2,575	2,959	3,225	3,780
91	1,321	1,888	2,250	2,573	2,957	3,222	3,776
92	1,320	1,887	2,248	2,571	2,954	3,219	3,773
93	1,318	1,885	2,246	2,569	2,952	3,216	3,770
94	1,317	1,884	2,244	2,566	2,949	3,214	3,767
95	1,316	1,882	2,242	2,564	2,947	3,211	3,764
96	1,315	1,881	2,241	2,562	2,944	3,209	3,761
97	1,314	1,879	2,239	2,560	2,942	3,206	3,758
98	1,313	1,878	2,237	2,558	2,940	3,204	3,755
99	1,312	1,876	2,236	2,556	2,938	3,201	3,752
100	1,311	1,875	2,234	2,555	2,936	3,199	3,750
102	1,309	1,872	2,231	2,551	2,931	3,194	3,744
104	1,308	1,869	2,228	2,547	2,927	3,190	3,739
106	1,306	1,867	2,225	2,544	2,923	3,186	3,734
108	1,304	1,864	2,222	2,541	2,919	3,181	3,729

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Table B.2 *(continued)*

Confidence = 95 %							
n	*p* = 0,750	*p* = 0,900	*p* = 0,950	*p* = 0,975	*p* = 0,990	*p* = 0,995	*p* = 0,999
110	1,302	1,862	2,219	2,537	2,916	3,177	3,724
112	1,301	1,860	2,216	2,534	2,912	3,173	3,720
114	1,299	1,858	2,213	2,531	2,909	3,170	3,715
116	1,298	1,855	2,211	2,528	2,905	3,166	3,711
118	1,296	1,853	2,208	2,525	2,902	3,162	3,707
120	1,295	1,851	2,206	2,522	2,899	3,159	3,703
122	1,293	1,849	2,203	2,520	2,896	3,155	3,699
124	1,292	1,847	2,201	2,517	2,893	3,152	3,695
126	1,291	1,845	2,199	2,514	2,890	3,149	3,691
128	1,289	1,843	2,197	2,512	2,887	3,146	3,687
130	1,288	1,842	2,194	2,510	2,884	3,143	3,684
132	1,287	1,840	2,192	2,507	2,881	3,140	3,680
134	1,286	1,838	2,190	2,505	2,878	3,137	3,677
136	1,284	1,837	2,188	2,503	2,876	3,134	3,674
138	1,283	1,835	2,186	2,500	2,873	3,131	3,670
140	1,282	1,833	2,185	2,498	2,871	3,128	3,667
142	1,281	1,832	2,183	2,496	2,868	3,126	3,664
144	1,280	1,830	2,181	2,494	2,866	3,123	3,661
146	1,279	1,829	2,179	2,492	2,864	3,121	3,658
148	1,278	1,827	2,177	2,490	2,861	3,118	3,655
150	1,277	1,826	2,176	2,488	2,859	3,116	3,652
152	1,276	1,825	2,174	2,486	2,857	3,114	3,650
154	1,275	1,823	2,172	2,484	2,855	3,111	3,647
156	1,274	1,822	2,171	2,483	2,853	3,109	3,644
158	1,273	1,821	2,169	2,481	2,851	3,107	3,642
160	1,272	1,819	2,168	2,479	2,849	3,105	3,639
162	1,272	1,818	2,166	2,477	2,847	3,102	3,637
164	1,271	1,817	2,165	2,476	2,845	3,100	3,634
166	1,270	1,816	2,163	2,474	2,843	3,098	3,632
168	1,269	1,815	2,162	2,473	2,841	3,096	3,630
170	1,268	1,813	2,161	2,471	2,840	3,094	3,627
172	1,267	1,812	2,159	2,469	2,838	3,092	3,625
174	1,267	1,811	2,158	2,468	2,836	3,091	3,623
176	1,266	1,810	2,157	2,466	2,834	3,089	3,621
178	1,265	1,809	2,155	2,465	2,833	3,087	3,619
180	1,264	1,808	2,154	2,464	2,831	3,085	3,616
185	1,263	1,805	2,151	2,460	2,827	3,081	3,611
190	1,261	1,803	2,148	2,457	2,823	3,077	3,607
195	1,259	1,801	2,146	2,454	2,820	3,073	3,602
200	1,258	1,798	2,143	2,451	2,816	3,069	3,598

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Table B.2 *(continued)*

Confidence = 95 %							
n	*p* = 0,750	*p* = 0,900	*p* = 0,950	*p* = 0,975	*p* = 0,990	*p* = 0,995	*p* = 0,999
205	1,256	1,796	2,140	2,448	2,813	3,065	3,593
210	1,255	1,794	2,138	2,445	2,810	3,062	3,589
215	1,253	1,792	2,136	2,442	2,807	3,059	3,585
220	1,252	1,790	2,133	2,440	2,804	3,055	3,581
225	1,251	1,789	2,131	2,437	2,801	3,052	3,576
230	1,250	1,787	2,129	2,435	2,798	3,049	3,574
235	1,248	1,785	2,127	2,432	2,795	3,046	3,571
240	1,247	1,783	2,125	2,430	2,793	3,043	3,568
245	1,246	1,782	2,123	2,428	2,790	3,041	3,564
250	1,245	1,780	2,121	2,426	2,788	3,038	3,561
255	1,244	1,779	2,120	2,424	2,786	3,036	3,558
260	1,243	1,777	2,118	2,422	2,783	3,033	3,555
265	1,242	1,776	2,116	2,420	2,781	3,031	3,553
270	1,241	1,775	2,115	2,418	2,779	3,028	3,550
275	1,240	1,773	2,113	2,416	2,777	3,026	3,547
280	1,239	1,772	2,111	2,415	2,775	3,024	3,545
285	1,238	1,771	2,110	2,413	2,773	3,022	3,542
290	1,238	1,770	2,109	2,411	2,771	3,020	3,540
295	1,237	1,768	2,107	2,410	2,769	3,018	3,538
300	1,236	1,767	2,106	2,408	2,767	3,016	3,535
310	1,234	1,765	2,103	2,405	2,764	3,012	3,531
320	1,233	1,763	2,101	2,402	2,761	3,008	3,527
330	1,232	1,761	2,098	2,400	2,758	3,005	3,523
340	1,230	1,759	2,096	2,397	2,755	3,002	3,519
350	1,229	1,757	2,094	2,395	2,752	2,999	3,515
360	1,228	1,756	2,092	2,392	2,749	2,996	3,512
370	1,227	1,754	2,090	2,390	2,747	2,993	3,509
380	1,225	1,752	2,088	2,388	2,744	2,990	3,505
390	1,224	1,751	2,086	2,386	2,742	2,988	3,502
400	1,223	1,749	2,084	2,384	2,739	2,985	3,499
425	1,221	1,746	2,080	2,379	2,734	2,979	3,493
450	1,219	1,743	2,077	2,375	2,729	2,974	3,486
475	1,217	1,740	2,073	2,371	2,725	2,969	3,481
500	1,215	1,737	2,070	2,368	2,721	2,965	3,476
525	1,213	1,735	2,067	2,364	2,717	2,961	3,471
550	1,212	1,733	2,065	2,361	2,713	2,957	3,466
575	1,210	1,731	2,062	2,358	2,710	2,953	3,462
600	1,209	1,729	2,060	2,356	2,707	2,950	3,458
625	1,208	1,727	2,058	2,353	2,704	2,947	3,455

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Table B.2 *(continued)*

Confidence = 95 %							
n	*p* = 0,750	*p* = 0,900	*p* = 0,950	*p* = 0,975	*p* = 0,990	*p* = 0,995	*p* = 0,999
650	1,207	1,725	2,056	2,351	2,702	2,944	3,451
700	1,204	1,722	2,052	2,347	2,697	2,939	3,445
750	1,202	1,719	2,049	2,343	2,692	2,934	3,439
800	1,201	1,717	2,046	2,339	2,688	2,930	3,434
850	1,199	1,715	2,043	2,336	2,685	2,926	3,430
900	1,198	1,712	2,040	2,333	2,682	2,922	3,426
950	1,196	1,711	2,038	2,331	2,679	2,919	3,422
1 000	1,195	1,709	2,036	2,328	2,676	2,916	3,418
1 500	1,186	1,697	2,022	2,312	2,657	2,895	3,394
∞	1,150	1,645	1,960	2,241	2,576	2,807	3,291

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Annex C
(informative)

Biological evaluation according to ISO 10993-1

C.1 General

According to ISO 10993-1, the following should be taken into account for their relevance to the overall biological evaluation of the NIS based on the nature and duration of their contact with the body:

a) the material(s) of manufacture;

b) intended additives, process contaminants and residues (see ISO 10993-7 for ethylene oxide residues);

c) leachable substances (see ISO 10993-17);

d) degradation products (see ISO 10993-9, for general principles and ISO 10993-13, ISO 10993-15 for degradation products from polymers and metals, respectively);

e) other components and their interactions in the final product;

f) the performance and characteristics of the final product;

g) physical characteristics of the final product, including but not limited to, porosity, particle size, shape and surface morphology;

h) identification of material chemical constituents and consideration of chemical characterization (see ISO 10993-18) shall precede any biological testing.

Unless the external surface of the primary container closure is in direct or indirect patient contacting (i.e. fits into one of the categories below), the biological reactivity of the materials of the primary container closure is not subject to ISO 10993-1.

The toxicity of materials that form the internal contact surfaces of the primary container closure is not addressed in this document. Health authority requirements and other toxicity requirements, including pharmacopeia/compendial requirements as appropriate, might apply. Such requirements can include ISO 10993-1 requirements.

C.2 Applicability to NIS

C.2.1 General

All testing indicated can be necessary for a biological safety evaluation, based on a risk assessment.

Additional tests might be required based on regional regulatory guidance (e.g. FDA Guidance on ISO 10993). Where sufficient information is already available to perform a risk assessment of the material and/or the medical device, additional testing is not required.

See ISO 10993-1:2018, Annex C for further guidance.

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C.2.2 Nature of body contact for NIS

C.2.2.1 Skin contact

NIS products might have components that contact the intact skin of the user, including adhesive for an OBDS affixed to the body (e.g. adhered), external surfaces of a NIS in contact with the user's ungloved hands (e.g. which might be touched or held during preparation and handling by the user) and/or components of the NIS in contact with the injection site. These materials can be considered surface contact materials - skin.

Some medical devices used in either sterile or non-sterile environments include components that can come in contact with a user's ungloved hands such as human interfaces. If these types of components can be shown to be made from materials in common use for other consumer products with a similar nature of contact, no further biological evaluation is needed.

C.2.2.2 Fluid path

If the NIS has a container and/or fluid path external to the primary container closure of the medicinal product, the materials that are part of the fluid path are considered external communicating – tissue/bone/dentin, as these materials serve as conduits to delivery fluids to subcutaneous/intramuscular tissue.

C.2.2.3 Indwelling needle or cannula

If the NIS contains an indwelling needle or soft cannula, the materials of this component are considered direct tissue contact (subcutaneous/intramuscular tissue).

C.2.3 Duration of exposure for NIS

Based on the intended use of the NIS, the duration of exposure is determined, considering single, multiple or repeated uses of the NIS.

Typically, a NIS with a use frequency of weekly, monthly or longer would be considered prolonged or long-term exposure.

According to ISO 10993-1, NIS components that have very brief/transitory contact with the body (e.g. used for less than one minute) are considered transitory-contact and generally would not require testing to address biocompatibility, unless the materials include coatings or lubricants that could be left in contact with body tissues after the contact ends; however, cumulative use should be considered as described above.

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Annex D
(informative)

Functional stability

D.1 General

This annex outlines the objective of performing functional stability, defines and discusses considerations for different types of products covered by this document. It is important to note that functional stability and transport are considered independent assessments and are not intended to be combined.

D.2 Functional stability (see 10.3.8)

D.2.1 General

Functional stability represents the overall lifetime of the product and includes the time that elapses from the point of manufacture of the final finished product, and release into the supply chain up through the point of first use (shelf-life) and the actual use of the product in the hands of users up to the point of last operational use and disposal (in-use life). Functional stability includes a combination of the shelf-life and the in-use life. The labelled shelf life (or expiration date) of the NIS is the date after which the NIS should not be used. The in-use life of the NIS represents the amount of time, uses and conditions which the NIS is labelled to be used for. The intent is that the NIS meets its primary functions at the end of its stated shelf and in-use life. Unless determined by risk assessment, it is expected that all testing will be performed on the NIS at standard atmosphere, not subjected to any preconditioning before testing.

D.2.2 Shelf-life

Shelf-life is determined by placing the NIS at the intended nominal storage conditions, with samples removed from the storage condition and tested at intermediate intervals through the labelled expiration date.

Ageing of the NIS to its expiration date can be accelerated through methods such as ASTM F1980, but should be confirmed through testing after real-time ageing.

D.2.3 In-use life

D.2.3.1 General

In-use life assessments are relevant for NIS with replaceable containers (system designations A and B), however, based on the intended use, design and risk assessment, in-use life can be applied to all NIS system designations.

D.2.3.2 NIS with replaceable container (system designations A and B)

For reusable NIS with replaceable container (system designations A and B), the in-use life is usually established or confirmed through testing their primary functions after simulated operation of each feature of the NIS (for example, cap and needle removal/attachment, injection, etc.) for 1,5 times the maximum expected number of actuations (including replacing containers) during its lifetime, unless the system is designed to stop working after a limited time or number of operations, which becomes the total number of operations adopted. Based on risk assessments, simulations to represent differences between labelled storage and use conditions (e.g. stored in refrigerator and used at room temperature)

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and required care (e.g. cleaning) performed between actuations can be incorporated into the in-use life assessments.

When the NIS is intended for use for multiple doses over a prescribed dosing period (i.e. one dose per day for 14 days) or delivery over an extended period (i.e. 10 ml over 2 hours), in-use life assessments include acceptable performance of the NIS and are usually confirmed through testing of the primary functions when used for the entire expected use in accordance with the labelling (the environment and duration of use).

The quality of the medicinal product should be ensured over the entire delivery duration per medicinal product requirements.

D.2.3.3 NIS with non-replaceable container (system designations C and D)

For NIS with non-replaceable container (system designations C and D), separate assessment of in-use life is not typically needed, as the in-use life can be established or confirmed through shelf-life testing (see D.2.2). However, based on the intended use, design, and risk assessment, further in-use life assessment should be considered (see D.2.3.2).

NISs with non-replaceable containers are considered to be prone to two separate mechanisms that can cause failure to meet primary functions. One is due to mechanical or electronic degradation during use and the other is time-related degradation during storage.

D.2.4 NIS component shelf-life

If it is determined by risk assessment that the performance or quality of NIS components or subassemblies might change over time, then the maximum warehouse storage time before assembly of these NIS components or subassemblies into a finished product should be established or confirmed. In order to accomplish this, these NIS components or subassemblies should be subjected to simulated storage conditions (at accelerated conditions, if possible, depending on materials of construction), then assembled into finished NIS. The finished NIS assembled from these aged components and subassemblies should meet their primary functions.

It is not usual practice for the life of finished medicinal product to be established or confirmed on products after formulation, filling or assembly from aged components (NIS components and sub-assemblies as well as excipients and primary packaging components). Confirmation of the shelf-life of the finished product with aged components and/or sub-assemblies should only be performed if required by risk assessment.

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Annex E
(normative)

Instructions for use, marking and age warning

E.1 Guidance in relation to the content of instructions for use

The instructions for use should contain, at a minimum, the below given information:

a) information provided in the markings on the NIS and NIS packaging, except for the information regarding the expiry date (if any), lot number, batch code or serial number, which can be omitted;

b) intended use: Information stating the purposes, use or uses, including users, patients and other conditions of use, for which the product is intended;

c) instructions for use: Instructions which have been validated to enable the intended users to use the product safely and for the purposes intended. Elements to be considered could include:

   1) instruction on the preparation, use and safe disposal of the product;

   2) inspection of the container and re-suspension of product;

   3) checking of the expiration date;

   4) any special storage or handling requirements;

   5) details that identify the NIS components and related equipment in order to obtain a safe combination;

   6) information in relation to re-use of the NIS, including container replacement, cleaning and disinfection;

   7) general trouble-shooting;

   8) any warnings and/or precautions to be taken;

   9) information required to safely use the NIS in its use environment, e.g. electrical NISs not be used close to area of electromagnetic radiation (such as mobile telephones in use), if the NISs are not specifically designed to be used in such areas;

   10) dosing information relevant to the NIS design (e.g. pre-set dose specifications, dose delivery status).

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E.2 Marking

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

a) name of the manufacturer;

b) details necessary in order for the user to identify the NIS (e.g. product name).

NOTE An alternative to the full name of the manufacturer can be sufficient identification (e.g. trademark or logo).

If any component intended to be removed of a NIS fits entirely into the small part cylinder shown in Figure 3 without compressing it and in any orientation, the NIS or component (if supplied separately),

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or their packaging or their relevant point-of-sale material, should be marked with the following or a similar statement:

“Warning! Keep away from children of 3 years and younger. Contains small parts.”

The indication of the hazard (i.e. “small parts”) should appear on the NIS or component (is supplied separately), on their packaging or in their instructions for use.

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Annex F
(informative)

Rationale for recommended sample sizes

F.1 General

The concepts for sample size determination described in the following aim to balance between the minimum sample size and the acceptable levels of risk and quality. The document specifies that each test result meets a minimum confidence interval, described by a confidence level and probability content.

A test can be performed as variable/ continuous test with variable result (e.g. measurement of a length) or as an attribute/discrete test (pass/fail) (e.g. colour of device is correct/incorrect, audible indication is present or not).

F.2 Variable testing

Variable testing can be used for measurement of continuous variables for which a continuous distribution can be used to describe the data either directly or after appropriate transformation.

At least a proportion of the population sampled indicated by p or probability content should meet the stated requirements with a specified confidence. Typically, a confidence of at least 95 % is used but this can be deviated from if it can be justified.

For variable tests where data can be treated as normally distributed (normally distributed or transformed to normal), the following are recommended sample sizes of n = 20 for 95 % probability content (p) and 95 % confidence, and n = 30 for 97,5 % probability content (p) and 95 % confidence.

The statistical calculations that should be used depend on the distribution, and the recommendations for variable testing are based on the normal, or Gauss, distribution. If a different distribution is used, the statistical calculations to justify the sample size should be performed.

The quantitative method presented here can only be used if the data are normally distributed or can be transformed to approximate the normal distribution.

It is allowed to choose other sample sizes than the recommended, but when using a sample other than the recommended one, it should be justified that the sample is sufficient and that it is adequately representative of the design.

In addition, when choosing a sample size different from the suggested sample size, the following should be considered:

— The smaller the sample size, the larger the sampling uncertainty, which can exaggerate small differences in the variability of the results and increase the risk of not meeting the probability content requirement for a given data set. When using k-values from a normally distributed population, this increase in uncertainty mandates a larger required k-value.

— The larger the sample size, the smaller the sampling uncertainty. This can potentially minimize the impact of small variances in the data and provide a better chance of meeting the probability content requirement at the specified confidence level. However, the increased sampling requirement might also result in higher costs in materials and testing time.

For data that can be described by the normal distribution, this document offers two ways of establishing acceptance criteria (see 7.4.5 for details).

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ISO 5479 provides guidance on methods and hypothesis testing for normality of data. It points out that it is not strictly necessary to use normality testing in each case if theoretical reasons or prior information supports normal distribution of data. Therefore, it is possible to leverage pre-existing justifications for normality or non-normality instead of performing a normality check on each new data set.

In addition, to minimize the testing costs and workload, in some cases multiple variables and attributes data can be captured on a single device. For example, with the right test equipment, one can capture delivered dose, injection time, needle extension and the presence of audible and visual indicators on one device. In these cases, the test lab should ensure that sufficient quantities of samples are present to meet the quality requirements for the variables and attribute measurements, which can require a larger sample than if only variables data were measured.

F.3 Attribute testing

Attribute tests can be used for assessment of discrete variables for which a discrete distribution can be used to describe the data either directly or after appropriate transformation.

Inspections and examinations will generally give discrete results such as “pass”, “fail”, or “inconclusive”. This can be transformed into a binomially-distributed data set by looking at the rate of one (or a group) of the results as a “success”. It is assumed that tests are assessed by looking at “pass” or “OK” results which are assumed to be binomially distributed (each inspection or examination is independent) and with a certain probability of success, or probability content, *p*.

For attribute testing a “zero defect acceptance plan” (or a defined number of acceptable failures) is used, which is modelled by means of a Chi Square distribution for later production testing or based on a simple binominal distribution for verification (as shown in this document).

For attribute testing, two categories, which can be both solved with a binominal distribution calculation, occur:

— statistical failure, (e.g. the presence or absence of audible indication, the failure only occurs randomly with a certain probability);

— systematic failure, (e.g. chemical tests failures will occur in all samples if there is a systematic error in the design).

The sample size calculation for both is based on a binomial distribution that is based on probability of failure, 1-*p*, and the acceptable confidence level.

The probability content (probability of success) is typically decided by the minimum failure rate that the test should be able to detect. If only systematic design failures are considered, the probability of failure of a single sample will be as much as 50 %, meaning every second part will be failing. For statistical failures, it depends on the established risk category, normally values from 1,0 % to - 5,0 % are used.

Table F.1 lists the recommended sample size for a binomial test accepting zero failures (a "zero defect acceptance plan") for different probability content levels and determined through one-sample proportion test. Note that the table includes more probability content levels than those used in the ISO 11608 series, these are provided for information only. The probability content levels in the highlighted rows are those used or assumed in the ISO 11608 series.

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Table F.1 — Recommended sample size for attribute tests (confidence level: 95 %)

Recommended sample size for attribute tests Based on a required confidence interval of at least 95 %	
Probability content (Probability of failure)	**Recommended sample size, *n* (min. samples size with 0 defects)**
$p \geq 0{,}999$ (0,1 %)	3 000 (2 995)
$p \geq 0{,}995$ (0,5 %)	600 (598)
$p \geq 0{,}990$ (1,0 %)	300 (299)
$p \geq 0{,}975$ (2,5 %)	120 (119)
$p \geq 0{,}950$ (5,0 %)	60 (59)
$p \geq 0{,}900$ (10,0 %)	30 (29)
$p \geq 0{,}850$ (15,0 %)	20 (19)
$p \geq 0{,}750$ (25,0 %)	11
$p \geq 0{,}500$ (systematic failure, 50,0 %)	5
$p \geq 0{,}050$ (Systematic failure 95,0 %)	1
NOTE 1 For the attributive aspect of doing visual inspections on samples used for life-cycle, damp heat, cyclical, and vibration, a probability content level of 85 % is employed. NOTE 2 Sample size numbers in parentheses are the exact sample size calculated from statistics. These numbers are derived directly from the binomial distribution and can be calculated for arbitrary probability content (p) and confidence level ($1 - \alpha$) using: $n = \text{roundup}(\ln(\alpha) / \ln(p))$. The recommended sample sizes are rounded to the nearest 10s for convenience, as also presented in test matrix (Table 3). This can mandate tests using multiple operators, due to length of testing. Caution should be used, however, since a failure in the samples above the minimum may jeopardize the ability to demonstrate performance to the desired level or probability and confidence and recovery can require many more units.	

F.4 Test selection flow chart

The following flow chart, Figure F.1, can be used to assist in the decision of how to treat test data. It is assumed that a variables test is preferable if the data supports this type of analysis as it provides more detailed knowledge of the design and requires a smaller sample size.

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