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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 the following URL: www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 84, *Devices for administration of medicinal products and catheters*.

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

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

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

Introduction

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

This document serves as the master standard and is the starting point for satisfying the requirements outlined in this and subsequent parts of the ISO 11608 series. As such, other parts should always be read and considered in conjunction with and subject to the provisions of this document and cannot be used as 'stand-alone' standards.

Because of the anticipated variation in the designs of NISs, this document is intended to be less prescriptive than previous editions. Thus, it tends to specify the results of the design effort instead of the physical and construction requirements used as the basis for NIS design, so that innovation in achieving the intended purposes is not unnecessarily restricted.

At the time of publication, the subsequent parts are:

— ISO 11608-2, *Needle-based injection systems for medical use — Requirements and test methods — Part 2: Needles*

— ISO 11608-3, *Needle-based injection systems for medical use — Requirements and test methods — Part 3: NIS containers and integrated fluid paths*

NOTE ISO 11608-3 has been renamed ("NIS containers and integrated fluid paths") and revised to better address the diversity of NIS containers (e.g. cartridges, syringes, flexible containers) that are either user-filled or manufacturer-filled. For user-filled containers, ISO 11608-3 includes test requirements for assessing materials in the fluid path (e.g. pyrogenicity, particulate matter) once filled. ISO 11608-3 also includes requirements for all containers related to system component interactions affecting the fluid path (e.g. seal integrity based on delivery forces, coring based on needle insertion).

— ISO 11608-4, *Needle-based injection systems for medical use — Requirements and test methods — Part 4: Needle-based injection systems containing electronics*

— ISO 11608-5, *Needle-based injection systems for medical use — Requirements and test methods — Part 5: Automated functions*

— ISO 11608-6, *Needle-based injection systems for medical use — Requirements and test methods — Part 6: On-body delivery systems*

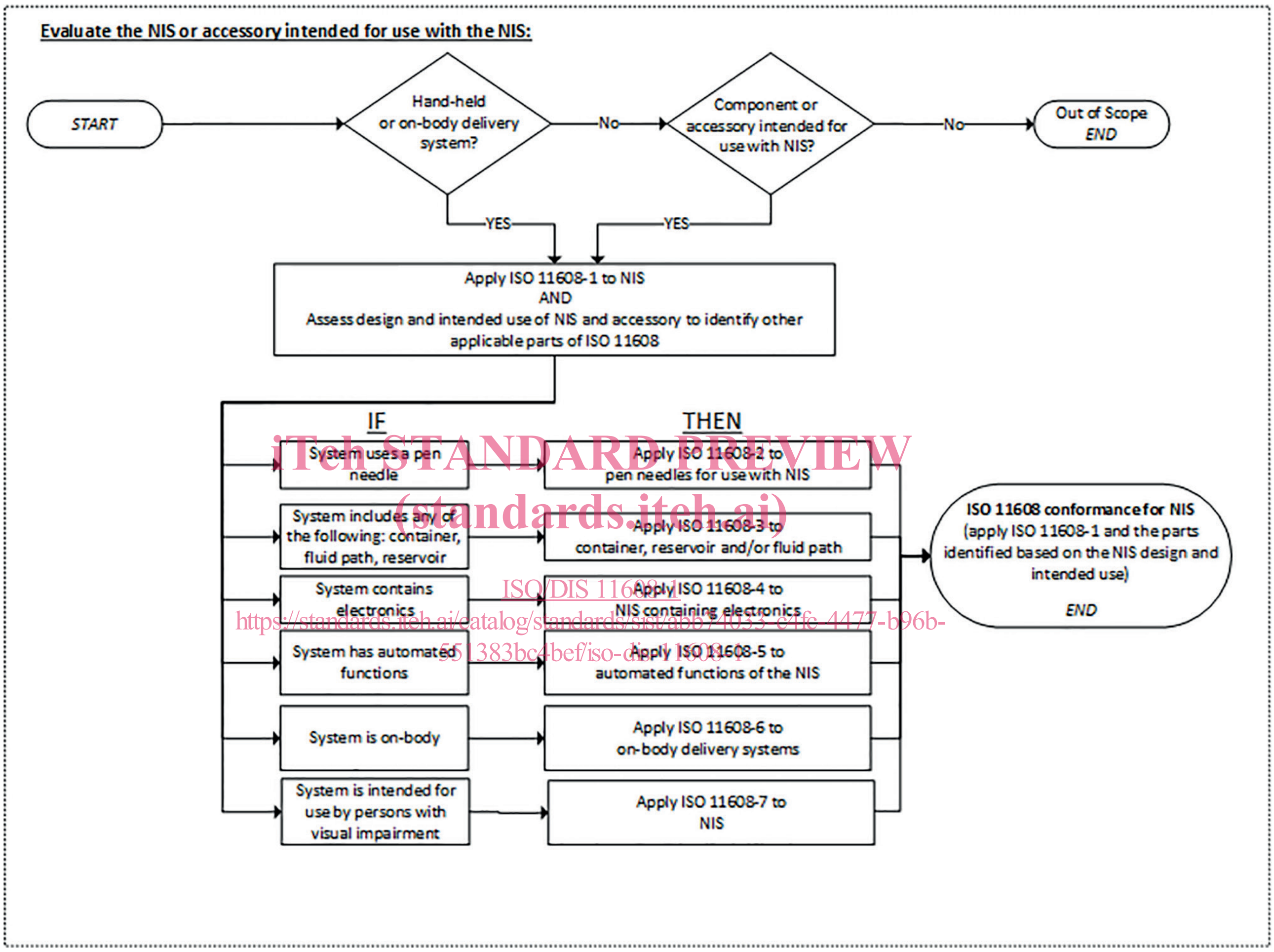
— ISO 11608-7, *Needle-based injection systems for medical use — Requirements and test methods — Part 7: Accessibility for persons with visual impairment.*

Figure 1 shows the relationship of this document to the other parts in the ISO 11608 series and offers a "road map" for consideration relative to which parts might apply to a specific NIS. Given this version's introduction of on-body delivery systems (OBDS in ISO 11608-6), additional terminology is being introduced to manage the distinctions between ISO 11608 NIS designs as well as avoid overlap with other NISs that are outside the scope of the ISO 11608 series.

NISs governed by ISO 11608 are defined as "hand-held" or "on-body" delivery systems (OBDSs). By hand-held, patients 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 60601-2-24:2012 Ed 2.0, ISO 28620:2010) 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 series includes requirements for design verification of the NIS's compliance 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 series is expanded to include 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.


Evaluate the NIS or accessory intended for use with the NIS:
START
Hand-held or on-body delivery system?
No
Component or accessory intended for use with NIS?
No
Out of Scope END
YES
YES
Apply ISO 11608-1 to NIS AND Assess design and intended use of NIS and accessory to identify other applicable parts of ISO 11608
IF
THEN
System uses a pen needle
Apply ISO 11608-2 to pen needles for use with NIS
System includes any of the following: container, fluid path, reservoir
Apply ISO 11608-3 to container, reservoir and/or fluid path
System contains electronics
Apply ISO 11608-4 to NIS containing electronics
System has automated functions
Apply ISO 11608-5 to automated functions of the NIS
System is on-body
Apply ISO 11608-6 to on-body delivery systems
System is intended for use by persons with visual impairment
Apply ISO 11608-7 to NIS
ISO 11608 conformance for NIS (apply ISO 11608-1 and the parts identified based on the NIS design and intended use)
END

NOTE If justified, other applicable requirements than those specified in the other parts of this standard series may be applied and conformity to this document can still be claimed.

Figure 1 — ISO 11608 road map

The design requirements related to system function are presented as a guide to assist manufacturers during the design phase. However, these design requirements do not replace system testing of the components and, where possible, direct communication and/or quality agreements between system component manufacturers.

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

There are other international and national standards and guidance publications and, in some countries, national regulations that are applicable to medical devices and pharmaceuticals. Their requirements supersede or complement this document. 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.

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

Finally, the document is written with the understanding that each system will be verified and validated for use with only one therapeutic or medicinal product. 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 shall be addressed individually according to the requirements of this document.

This document is expected to be supplemented by additional requirements and might occasionally be superseded by such regulatory authorities.

Guidance on transition periods for implementing the requirements of this document is given in ISO/TR 19244.

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, through needles or soft cannulas for intradermal, subcutaneous and/or intramuscular delivery, incorporating pre-filled or user-filled, replaceable or non-replaceable containers.

Stand-alone prefilled syringes defined by ISO 11040-8 are not covered by this document (see exclusions below). However, when the prefilled syringes are provided to the user with an integrated addition, certain portions of the ISO 11608 series apply as follows:

— prefilled syringes that are provided to the user with an integrated electronic addition (e.g. electronic dose counter) are covered by relevant requirements of ISO 11608-4, but only to assess the function, feature or performance of the “addition” not the prefilled syringe;

— prefilled syringes that are provided to the user with an integrated addition that provides an automated function (e.g. an automated inserter that inserts to a predetermined insertion depth or needle safety device) are covered by relevant requirements of ISO 11608-5, but only to assess the function, feature or performance of the “addition” (as integrated into the NIS) not the prefilled syringe.

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);

— toxicity (biocompatibility) of materials that form the medicinal product contact surfaces of the primary container closure;

— 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);

— containers that can be refilled multiple times;

— needle-free injectors;

— requirements relating to methods or equipment associated with user filling of containers unless they are dedicated accessories;

— NISs intended for dental use;

— syringes and needles which are not intended for use in a NIS;

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

NOTE These exclusions might benefit from elements in this document but might not completely fulfil the basic safety and effectiveness of those 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 11608 (all parts), *Needle-based injection systems for medical use — Requirements and test methods*

ISO 13485:2016, *Medical devices — Quality management systems — Requirements for regulatory purposes*

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

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

EN 71-1:2014+A1:2018, *Safety of toys – Mechanical and physical properties*

3 Terms and definitions

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

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

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

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

3.1
accessory
article or supplementary part used in conjunction with a *NIS* (3.15)

3.2
container
components of the *NIS* (3.15) used to hold the medicinal product

Note 1 to entry: Containers may be integrated into the *NIS* (3.15) at the point of manufacture or assembled into the *NIS* (3.15) at the time of use.

Note 2 to entry: The container may 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.

3.3
deliverable volume
contents of the *container* (3.2) which could be expelled by operating the *NIS* (3.15) in accordance with the *instructions for use* (3.10)

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

3.4
design specification
functional, performance, usability or safety characteristic of a NIS, developed from design inputs, that is confirmed during design verification

3.5
dose delivery efficiency
ratio of expelled volume to fill volume

Note 1 to entry: Delivery efficiency can be used to evaluate *dose accuracy* (3.6) for *NISs* (3.15) designed to fully empty single-dose containers filled by the user.

3.6
dose accuracy
difference between the intended dose and the delivered dose

3.7
dose delivered indication
feedback given to the user to indicate the amount of medicinal product delivered

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

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

3.8
fluid path
pathway the medicinal product follows from the *container* (3.2) to the targeted delivery site

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

3.9
functional stability
ability of a *NIS* (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 *NIS* (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 NIS maintains *primary functions* (3.18), when used in accordance with 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* (3.19) through its last dose delivered.

3.13
manufacturer-filled
container (3.2) pre-filled with the medicinal product by the manufacturer

Note 1 to entry: Such containers are also referred to as the *primary container closure* (3.17). See ISO 11608-3:20##, Annex F.

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

3.14
minimum deliverable dose
for *NIS* (3.15) with system designations B1 and D1 filled by the manufacturer, the minimum dose the system is able to deliver

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

Note 1 to entry: This term may also be referred to as “system” in this document.

3.16
pre-setting
procedure by which individual amounts of medicinal product can be selected for injection by the user

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

3.17
primary container closure
PCC
container (3.2) 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 *NIS* (3.15), which, if it does not perform to specifications during use, would result in a failure to accurately deliver the medicinal product via the correct route and/or 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* (3.6). 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 *NIS* (3.15) ready for use (e.g. removing air from the fluid path)

3.20
reservoir
container (3.2) supplied empty and which 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 11608-3:20##, Annex F.

3.21
residual volume
volume of medicinal product remaining within the *NIS* (3.15), after dose delivery has been completed

Note 1 to entry: In the case of a *NIS* (3.15) which 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 *NIS*s (3.15)).

3.22
residual scale (optional)
scale which indicates the remainder of medicinal product in the *container* (3.2)

3.23
shelf life
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 NIS by whether the (medication) container is replaceable or non-replaceable, and if that container is intended to contain multiple doses or a single dose

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

3.25
user-filled
container (3.2) filled or reconstituted (e.g. if in lyophilized form) via a manual or automated process by the user from a separate medicinal product or diluent container

4 Symbols and abbreviated terms

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:

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

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 accuracy measurements, *n*, conducted at each dose setting. The k-value is found in Annex B

DR Dialling resolution, the minimum dose setting increment of the NIS

⟨ Absolute error, in millilitres, used to define the upper and lower specification limits for a pre-set dose in absolute terms

® Relative error, as a percentage, used to define the upper and lower specification limits for a pre-set dose in relative terms

TP The transition point volume, in millilitres, at which the upper and lower specification limits for V_{set} change from absolute terms to relative terms:

TP = (100 ×α)/β

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

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

5 Requirements

5.1 General

5.1.1 In addition to the requirements of this document, other parts of ISO 11608 shall be fulfilled where applicable (see Figure 1 for guidance). If justified, other applicable requirements may be applied and conformity to this document can be claimed.

5.1.2 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.

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

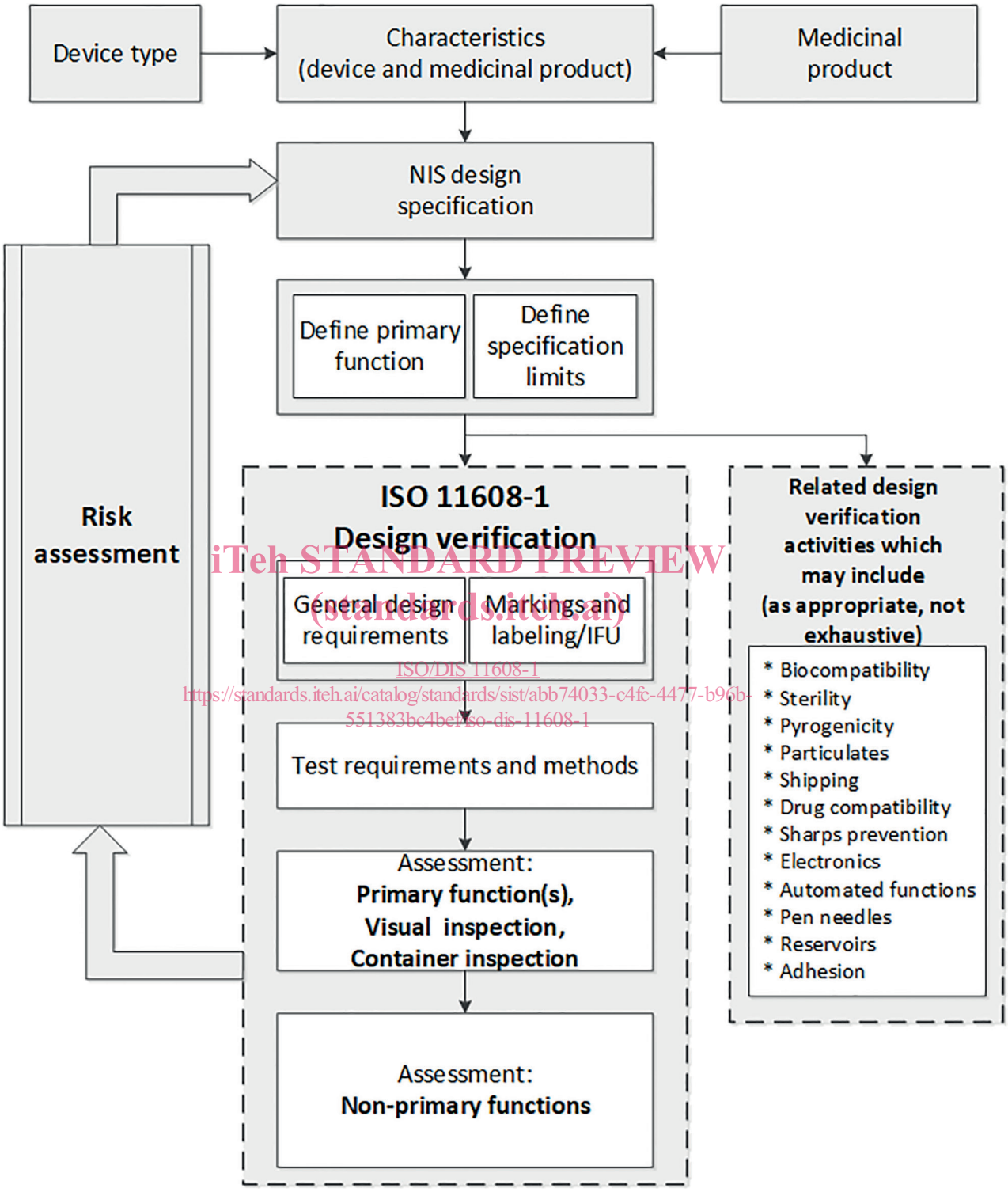


Figure 2 — Design verification flow

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.