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

Part 6:
On-body delivery systems

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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*.

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

The ISO 11608 series has traditionally addressed hand-held needle-based injection systems (NISs) that are intended for parenteral administration by injection of medicinal products through a needle to humans. These injections are performed manually, through exertion of force by the user, or automatically through use of an internal power source through a needle into the patient's tissue.

NOTE Although technically a device using a soft cannula is not "needle-based", the cannula is placed by a needle and can be included in this classification.

The user typically places the hand-held NIS at the injection site and holds the NIS in place until the injection has completed. The intended use and delivery requirements of some medicinal products can make manual manipulation and stabilization of a hand-held NIS during the medicinal product delivery process impractical or impossible, and can result in an incomplete dose, missed dose, or user injury. For example, it might not be appropriate, practical or possible for users to hold a NIS in place for an extended period of time required by the volume or viscosity of the medicinal product or required to preclude patient discomfort.

Delivery systems that are affixed to the body of the user eliminate some of the risks associated with delivery of medicinal product through a traditional NIS. This document provides a consistent method for evaluating the unique requirements and risks associated with these systems, herein referred to as "on-body delivery systems" (OBDS).

Similarly to ISO 11608-1 and ISO 11608-5, this document will tend to specify the results of the design effort instead of the physical and construction requirements used as the basis for OBDS design, so that innovation in achieving the intended purposes is not unnecessarily restricted.

NISs governed by the ISO 11608 series are defined as "hand-held" or "on-body" delivery systems (OBDSs). When 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 backpack or pocket).

In either configuration, the time or speed employed to deliver a discrete volume would be based upon patient tolerability or patient convenience rather than clinical relevance (e.g. medication efficacy) as would be the case with insulin patch pumps or traditional infusion pumps associated with continuous delivery (e.g. insulin).

This document only addresses the basic safety and performance of the product and manufacturers can through risk assessments, identify additional requirements due to the unique nature of their specific system or application.

The sampling plans for inspection selected for this document and outlined in ISO 11608-1 are intended to verify the design, at a high confidence level. The sampling plan does not replace the more general manufacturing quality systems, including lot release, which appear in International Standards on quality systems, e.g. ISO 9001 or ISO 13485.

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 6: On-body delivery systems

1 Scope

This document specifies requirements and test methods for On-Body Delivery Systems (OBDS) needle-based injection systems (NISs) for single patient use, intended for subcutaneous, intramuscular or intradermal delivery of a discrete volume (bolus) of medicinal product, through needles or soft cannulas, incorporating pre-filled or user-filled, replaceable or non-replaceable containers.

NOTE 1 Although technically a device using a soft cannula is not "needle-based", the soft cannula is placed by a needle and can be included in this classification.

NOTE 2 Some requirements and methods are already established and included in other parts of the ISO 11608 series.

Infusion pumps that are designed for continuous delivery at a specific rate required to achieve and/or maintain a desired plasma medicinal product concentration are excluded from this document. However, while this document is not intended to directly apply to these pump products, it does contain requirements and test methods that can be used to help design and evaluate them.

NOTE 3 They are covered by IEC 60601-2-24 (if electronic) or ISO 28620 (if non-electronic).

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 11608-1:2021, *Needle-based injection systems for medical use - Requirements and test methods - Part 1: Needle-based injection systems*

ISO 11608-3:2021, *Needle-based injection systems for medical use - Requirements and test methods - Part 3: NIS containers and fluid paths*

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*

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:

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

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

3.1
body-worn on-body delivery system
body-worn OBDS
on-body delivery system (3.7) that is directly adhered to the skin

3.2
dose accuracy
measure of the total volume of medicinal product delivered to the patient

3.3
dose delivery time
measure of the total time over which the total dose volume is delivered

3.4
dose delivery profile
plot of the volumetric output of the *on-body delivery system* (3.7) against unit time throughout the duration of the delivery

3.5
leakage
escape of medicinal product from the *on-body delivery system* (3.7) other than from the patient end of the fluid path during delivery

3.6
needle extension
axial distance from the patient end of the needle or soft cannula tip to the nearest part of the *on-body delivery system body* (3.8)

Note 1 to entry: See ISO 11608-5:2021, Figures C.1 to C.7 for 90-degree insertion and less than 90-degree insertion.

3.7
on-body delivery system
OBDS
delivery system, which is affixed to the body of the user that actively delivers medicinal product, and includes the medicinal product container and components for administration through a needle or soft cannula

3.8
on-body delivery system body
OBDS body
defining the point of contact with the patient adjacent to the injection site

3.9
occlusion
blockage or closing of fluid path of *on-body delivery system* (3.7) during drug administration that is not part of the intended use

3.10
patient tolerability
level to which pain, discomfort and other effects experienced during use of the *on-body delivery system* (3.7) are accepted by patients

3.11
patient-worn on-body delivery system
on-body delivery system (3.7) that is attached over or under patient's clothes, but not directly adhered to the skin

Note 1 to entry: This type of injector is attached to the patient through tubing and a catheter.

4 Requirements

4.1 General

The requirements of ISO 11608-1:2021, 5.1 shall apply.

4.2 Risk assessment

The requirements of ISO 11608-1:2021, 5.3 shall apply.

For OBDS, a Safety Assurance Case (SAC) (for example, developed using recommendations such as those in AAMI/TIR 38) may be used to fulfil the ISO 14971 requirement for a risk management report.

4.3 Usability engineering

The requirements of ISO 11608-1:2021, 5.4 shall apply.

4.4 Uncertainty of measurement and conformance with specifications

The requirements of ISO 11608-1:2021, 5.5 shall apply.

4.5 General design requirements

Applicable requirements of ISO 11608-1:2021, 5.6 shall apply.

4.6 Physical or mechanical requirements and test methods

4.6.1 General

Unless otherwise specified, the testing shall be performed at standard atmosphere as specified in ISO 11608-1. For OBDS, manufacturers shall determine the temperature range of the OBDS and drug during delivery (which may be impacted by body temperature). In use testing, and testing of drug compatibility should be completed throughout that temperature range.

4.6.2 Systems comprising rigid needles

In addition to the requirements in ISO 11608-3, additional physical and functional evaluations shall be considered, e.g. flexural fatigue. Risk assessment shall be used to determine appropriate evaluations.

4.6.3 Systems comprising a soft cannula(s)

The requirements of ISO 11608-3 shall apply.

4.6.4 Leakage from the OBDS

The OBDS shall be inspected for leakage when tested in accordance with ISO 11608-1 in at least worst-case environments and orientations representative of the expected use. Any amount of leakage observed during testing shall be assessed for its ability to impact OBDS performance, fluid path or medicinal product sterility, or risk to humans or the environment.

Any allowable leakage shall be addressed by risk assessment and appropriate information shall be provided to the user in the instructions for use.

If any preconditioning creates the appearance of condensation or any other external evidence of fluid, the manufacturer shall assess and confirm that this was not medicinal product leakage.

4.6.5 Means of attachment

The developer of the OBDS shall establish performance criteria to ensure that the means of attachment to the body is adequate to maintain a reliable medicinal product delivery pathway.

If the means of attachment uses adhesive, the following apply:

— attachment of the OBDS to the adhesive patch and the adhesive to the body are adequate to maintain reliable medicinal product delivery pathway;

— if odour control, MVTR (moisture vapour transmission rate), water resistance or impermeability, absorbency or conformity have been identified requirement for the OBDS, the adhesive material should be tested for these properties.

Conduct adhesion/attachment tests when used as specified in the instructions for use. Where the OBDS shall be maintained in a specific orientation, visually confirm that the OBDS maintains the required orientation during testing. If an adhesive is used, see Annex A, which contains suggested test methods for verifying the functional performance of an adhesive. It is up to the manufacturer to identify suitable tests from those suggested or to develop their own test.

Testing of adhesion/attachment shall also measure performance of the OBDS under conditions consistent with the intended use of the product, which may include exposure to typical fluids that can be encountered during use (e.g. water, personal cleaning products, deodorants, skin lotion, medical alcohols, perspiration) including the medicinal product, if appropriate. Adhesive tests may be performed on material that has undergone sterilization or aging if it is anticipated through the risk analysis that the adhesive property will be adversely affected by such conditioning. Based on risk assessment, additional evidence might be required to demonstrate the performance and safety of the means of attachment. This may include use on humans under simulated conditions of actual use (not necessarily including the actual delivery). This evidence may also need to confirm that the adhesive bond between the OBDS and the user does not cause unacceptable tissue trauma (as defined by risk assessment) or create a bond that is too difficult for the user to remove. It is recognized that in some cases, reference to existing clinical and/or other evidence may be sufficient to demonstrate performance of the means of attachment.

The factors that affect Medical Adhesive Related Skin Injuries (MARSI) are complex and related to factors that the OBDS manufacturer can control (adhesive properties, design of patch geometry, suggested application points, etc.) and factors that the OBDS manufacturer cannot control (patient population, removal technique, etc.).[74] The selection of the adhesive should show due consideration for the risk of MARSI to the end user balanced against the performance requirements of the OBDS, applying risk control, where practicable.

Extended wear can result in the adhesive developing a stronger bond over time, which could impact the patient. This should be considered and addressed in the testing.

4.6.6 Occlusion

The potential harm to the patient of a partial or complete occlusion resulting in a reduction or cessation of delivery, or delivery of a fast bolus upon clearance of the occlusion, shall be determined, and the risk based on the criticality of the medicinal product shall be addressed in the risk assessment. If required, appropriate control(s) (design and/or indicator, instruction for use etc.) shall be implemented, which may include a mechanism for the user to determine the ongoing status of the delivery (i.e., a delivery indicator).

NOTE 1 Occlusion might lead to OBDS not meeting its primary function such as dose accuracy or delivery time. The clearance after occlusion might lead to an instantaneous fast injection that might adversely impact the patient.

NOTE 2 Delivery indication can be done by audible or tactile means or visually by an analogue or digital indicator.

4.7 Functional performance requirements and test methods

4.7.1 General

In addition to the conditioning specified in ISO 11608-1, manufacturers shall evaluate if simulating additional conditions to which the OBDS is subjected as worn before and/or during delivery (e.g. "normal/anticipated conditions" from ISO 11608-1) when testing primary functions is appropriate. These additional test conditions shall be based on the risk analysis (e.g. due to the potential for extended dose delivery time and warming of the OBDS while affixed to the body). Potential conditions to consider include the following:

— vibration;

— temperature;

— humidity;

— atmospheric pressure;

— light exposure;

— orientation.

Each additional test shall be carried out at conditions that simulate the operation of the OBDS.

NOTE Primary functions can be able to be assessed during the same testing protocol and on one set of samples.

4.7.2 Dosing requirements and methods

4.7.2.1 General

There are three measurements relevant to the dosing of OBDS:

— dose accuracy;

— dose delivery time;

— dose delivery profile.

At a minimum, dose accuracy is considered a primary function. Risk assessment shall determine whether dose delivery time is considered a primary function, in accordance with ISO 11608-1.

4.7.2.2 Dose accuracy

The dose accuracy (dose delivered) shall be verified by measuring the total dose delivered. Where the dose is specified as discontinuous dosing segments, dose accuracy shall be assessed for each dose segment, including last dose accuracy (for variable dose OBDS) and dose delivery efficiency for user filled OBDS.

If the OBDS is intended to be paused or stopped by the user (i.e., delivery volume during pause = 0), then the dose accuracy testing at standard atmosphere conditions shall include this state to ensure that the accuracy of the dose delivered shall not be adversely affected by any planned interruption (pause/stop feature on OBDS) of the dose. Based on the risk assessment, the manufacturer shall determine if assessment of the dose accuracy including the pause/stop feature is required after any additional pre-conditionings besides standard.

Dose accuracy testing should be performed under conditions that simulate in vivo tissue back pressure, if this is determined to be relevant through risk assessment.