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

Part 6: On-body delivery systems

Systèmes d'injection à aiguille pour usage médical — Exigences et méthodes d'essai —

Partie 6: Systèmes d'administration sur le corps

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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.

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 11608-1:2022, *Needle-based injection systems for medical use - Requirements and test methods - Part 1: Needle-based injection systems*

ISO 11608-3:2022, *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 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 http://www.electropedia.org/

3.1
clinically relevant
related to patient tolerability (e.g. injection site reaction such as pain, swelling redness) or to the safety or effectiveness of the drug to be delivered

Note 1 to entry: If the safety or effectiveness of the drug to be delivered could be adversely impacted by significant variations in the delivery profile, then these shall be considered in the risk-based determination of allowable variation.

3.2
body-worn on-body delivery system
body-worn OBDS
on-body delivery system (3.8) that is directly adhered to the skin

3.3
dose accuracy
measure of the total volume of medicinal product delivered to the patient

3.4
dose delivery time
measure of the total time over which the total dose volume is delivered

3.5
dose delivery profile
plot of the volumetric output of the *on-body delivery system* (3.8) against unit time throughout the duration of the delivery

3.6
leakage
escape of medicinal product from the *on-body delivery system* (3.8) other than from the patient end of the fluid path during delivery

3.7
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* (3.9)

Note 1 to entry: See ISO 11608-5:2022, Figures C.1 to C.7 for 90-degree insertion and less than 90-degree insertion.

3.8
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

3.9
on-body delivery system body
OBDS body
defining the point of contact with the patient adjacent to the injection site

3.10
occlusion
blockage or closing of fluid path of *on-body delivery system* (3.8) during drug administration that is not part of the intended use

3.11
patient tolerability
level to which pain, discomfort and other effects experienced during use of the *on-body delivery system* (3.8) are accepted by patients

3.12
patient-worn on-body delivery system
patient-worn OBDS
on-body delivery system (3.8) 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 11608-1:2022, 5.1 shall apply.

4.2 Risk assessment

The requirements of ISO 11608-1:2022, 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 11608-1:2022, 5.4 shall apply.

4.4 Uncertainty of measurement and conformance with specifications

The requirements of ISO 11608-1:2022, 5.5 shall apply.

4.5 General design requirements

Applicable requirements of ISO 11608-1:2022, 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.).[73] 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.

4.7.2.3 Dose delivery time

Dose delivery time is a measure of the time over which the total (or each if there are multiple dose segments) dose is delivered.

Design verification of the required dose delivery time, determined by risk assessment, shall be performed in accordance with ISO 11608-5.

The dose delivery time shall be verified by measuring the time over which the total dose is delivered. Where the dose is specified as discontinuous dosing segments, the time of the delivery of each dose segment shall be measured.

If the OBDS is intended to be paused or stopped by the user (i.e., delivery volume during pause = 0), then the testing of the dose delivery time at standard atmosphere conditions shall include this state to ensure that the time over which the dose is delivered is not 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 time of the dose delivered including the pause/stop feature is required after any additional pre-conditionings besides standard.

4.7.2.4 Dose delivery profile

In instances where the dose delivery profile is determined to be clinically relevant, the manufacturer shall characterize and set acceptable limits for variability for the dose delivery profile. The final OBDS shall be verified to deliver the medicinal product consistent with the defined profile.

The dose delivery profile provides insight into the relationship of the dose volume delivered over the dose delivery time.

It can be helpful to characterize the dose delivery profile as part of the design and development of any OBDS/medicinal product combination, regardless of clinical relevance.

See Annex B for guidance and potential methods for the measurement of dose profile, possible ways to plot the dose profile and suggested methods for setting limits of variability.

4.7.3 Sharps injury protection

In case sharp injury protection features are claimed, the requirements specified in ISO 23908 shall apply.

4.7.4 Automated functions

Where the OBDS includes automated functions, the requirements and test methods in ISO 11608-5 apply.

4.7.5 Injection depth and needle extension

4.7.5.1 Needle and cannula insertion distance measurement and damage inspection

After deployment of the needle or cannula, measure the extension distance. For soft cannulas, confirm by visual inspection that the soft cannula has no damage (splitting, cracking, distortion etc.). Extension measurement and inspection may be conducted before, during or after dose delivery if it can be determined that the extension distance does not change during delivery.

If, according to risk analysis, a significant risk of damage to the soft cannula caused by the influence of skin tissue is identified, then visual inspection for damage to the soft cannula shall be conducted following insertion into a representative skin tissue model, retraction of the introducer and withdrawal of the soft cannula.

4.7.5.2 Needle/cannula displacement during use

Manufacturers shall assess needle and/or soft cannula displacement of the OBDS to confirm that the needle and/or cannula remains within the intended anatomical space for the defined duration and wear period and during ambulatory activities (as defined in the instructions for use). Such assessment shall be risk-based and can require confirmation testing through in vitro models or clinical evidence (i.e. OBDS attachment displacement, injection site leakage, pharmacokinetic effect, etc.).

NOTE See also Annex C.

4.8 Biological requirements of the OBDS

4.8.1 Sterility of OBDS

The requirements of ISO 11608-3:2022, 4.5.6 shall apply.

4.8.2 Biocompatibility

The requirements of ISO 11608-1:2022, 5.6 p) shall apply. See also ISO 11608-1:2022, Annex C.

4.9 Medicinal product compatibility

4.9.1 General

The requirements of ISO 11608-3:2022, 4.5.1 and 4.5.2 shall apply.

4.9.2 Particulates

The requirements of ISO 11608-3:2022, 4.5.3 shall apply.

4.9.3 Pyrogenicity

The requirements of ISO 11608-3:2022, 4.5.4 shall apply.

4.9.4 Extractable/leachables

The requirements of ISO 11608-3:2022, 4.5.5 shall apply.

4.10 Electrical safety and software requirements

4.10.1 Electrical safety

For OBDSs containing electronics, the applicable clauses of ISO 11608-4 for additional considerations and requirements necessary to ensure electrical safety shall apply.

4.10.2 Software

For OBDSs containing software (which includes firmware), the applicable clauses of ISO 11608-4 for additional considerations and requirements necessary to address software considerations shall apply.

5 Inspection

Inspection shall be carried out in accordance with ISO 11608-1:2022, Clause 11.

6 Information supplied by the manufacturer

The requirements of ISO 11608-1 shall apply. In addition, appropriate information regarding leakage in accordance with 4.6.4. shall be provided to the user in the instructions for use.

Annex A
(informative)

Test methods for adhesion

Functional performance of an adhesive may be verified through various test methods. See Table A.1 for available test methods to measure adhesive properties of tack, peel and shear. Tack is most relevant for pressure sensitive adhesives and is a measure of how quickly a bond is formed. Peel is a measure of the force needed to break the bond between an adhesive tape and the surface it's been applied to. Shear measures the durability of the bond by measuring the time that it takes for a vertically mounted sample to slip off the substrate.

See Table A.1 for available test methods for adhesion.

Table A.1 — Test methods to measure adhesive properties

		ASTM[a]	EN and ISO[b]	PSTC[C]
Tack	Loop	D6195-03	EN 1719	PSTC-16
	Rolling Ball		EN 1721	PSTC-6
	Probe	D2979-01	-	-
Peel	180°	D3330/D3330M-04	EN 1939	PSTC-101
	90°	D3330/D3330M-04	EN 1939	PSTC-101
	T-Test	D1876-08	ISO 11339	-
Shear	Static	D3654	EN 1943	PSTC-107
	Dynamic	-	ISO 4587	-
MVTR		-	EN 13726-2	-

[a] American Society for Testing and Materials

[b] European Standards (EN) and International Standards (ISO)

[c] Pressure Sensitive Tape Council

Additional test methods for information:

— ASTM D903 on peel or stripping strength of adhesive bonds ;

— ASTM F2256 on strength properties of tissue adhesive by t-peel loading;

— ASTM D1002 on adhesive lap joint shear strength test;

— ASTM F2258 on tensile strength of tissue adhesives;

— ASTM F2458 on wound closure strength of tissue adhesives.

Annex B
(informative)

Dose delivery profiles

B.1 General dosing characteristics

There are three characteristics of OBDS that are relevant to dosing: dose accuracy, dose delivery time and dose delivery profile. This annex only addresses the dose delivery profile.

B.2 General dose delivery profile

The dose delivery profile provides insight into the relationship of the dose volume delivered over the dose delivery time. As part of the risk assessment, the dose profile can be determined to be clinically relevant. Where the profile is determined to be clinically relevant, the delivery profile is characterized, acceptable limits for variability are established and the ability of the final OBDS to deliver the medicinal product consistent with the defined profile verified.

Regardless of clinical relevance, it may be helpful to characterize the dose delivery profile as part of the design and development of all OBDS/medicinal product combinations. During development, the dose delivery profile can help in understanding the reasons and expectations for the variability of the OBDS performance, particularly for OBDSs with larger delivery volumes and longer delivery times.

B.3 Measurement of dose delivery profile

Delivery from an OBDS can be measured and characterized by recording the volume delivered (typically by gravimetric measurement and conversion to volume using the density of solution or suspension) at specific times during the delivery. The time intervals at which each measurement is taken should consider the total delivery time, the technology of the OBDS (e.g. constant force vs. constant displacement) and, if defined, the profile limits.

The dose profile from this type of measurement can be represented in a bar chart, by plotting the volume of each aliquot of the solution (or suspension) collected [incremental volume (V)] at each time point against time (t). This type of dose profile is represented in Figures B.1 and B.2. These are examples of a delivery profile for delivery of a nominal volume of 10 ml and a nominal delivery time of 25 min with incremental volume, V, recorded every 0,5 min.

Figures B.1 and B.2 show two types of maximum dose profile limits. See B.5 for setting specification limits.

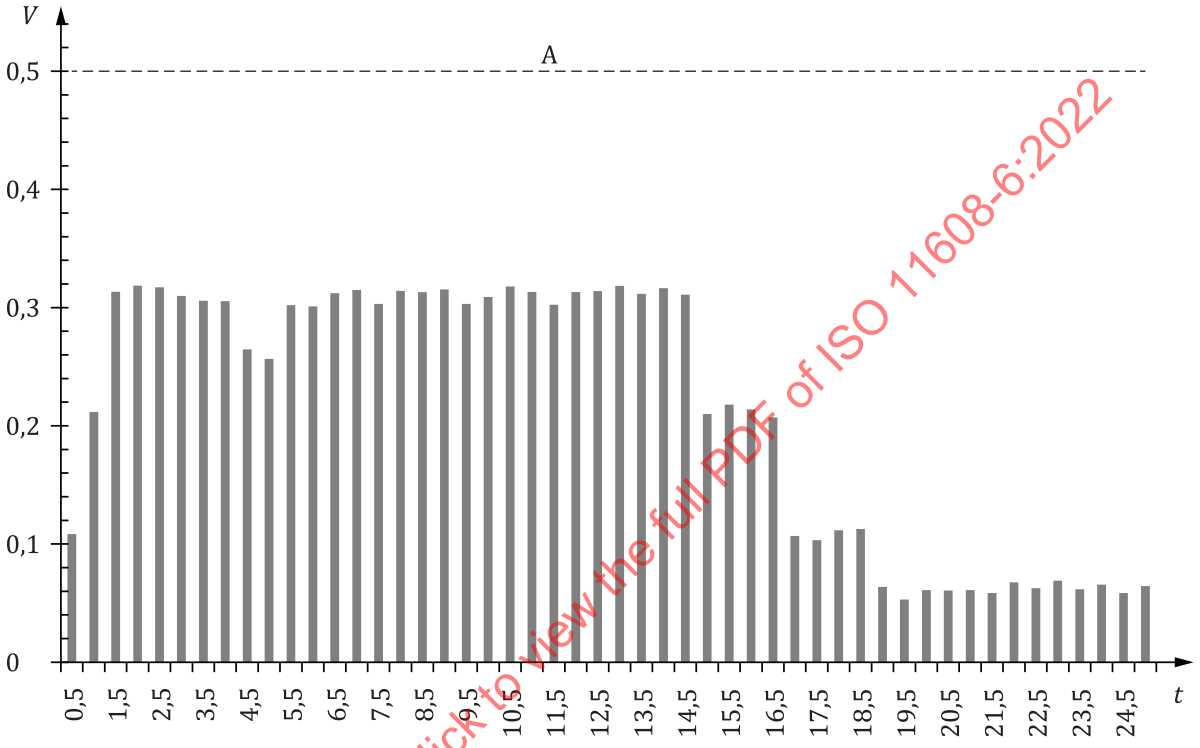
Alternatively, these measurements can be represented as a line chart, by plotting the cumulative volume at each time point. This type of dose profile is represented in Figure B.3. This is another example of a delivery profile for delivery of a nominal volume of 10 ml and a nominal delivery time of 25 min with incremental volume, V, recorded every 0,5 min.

The data points and limits shown in these examples are for illustration only and each manufacturer shall consider and set limits appropriate for each OBDS/medicinal product combination.

B.4 Plotting of dose delivery profile

B.4.1 Individual volume measurements against time – Bar charts

The dose profile can be displayed as a bar chart showing a plot of incremental volumes measured from the start until the end of delivery, collected by using a method as described in B.4. Each data point represents the incremental volumes measured at that time since the previous measurement. This type of dose profile is represented in Figure B.1 and B.2.



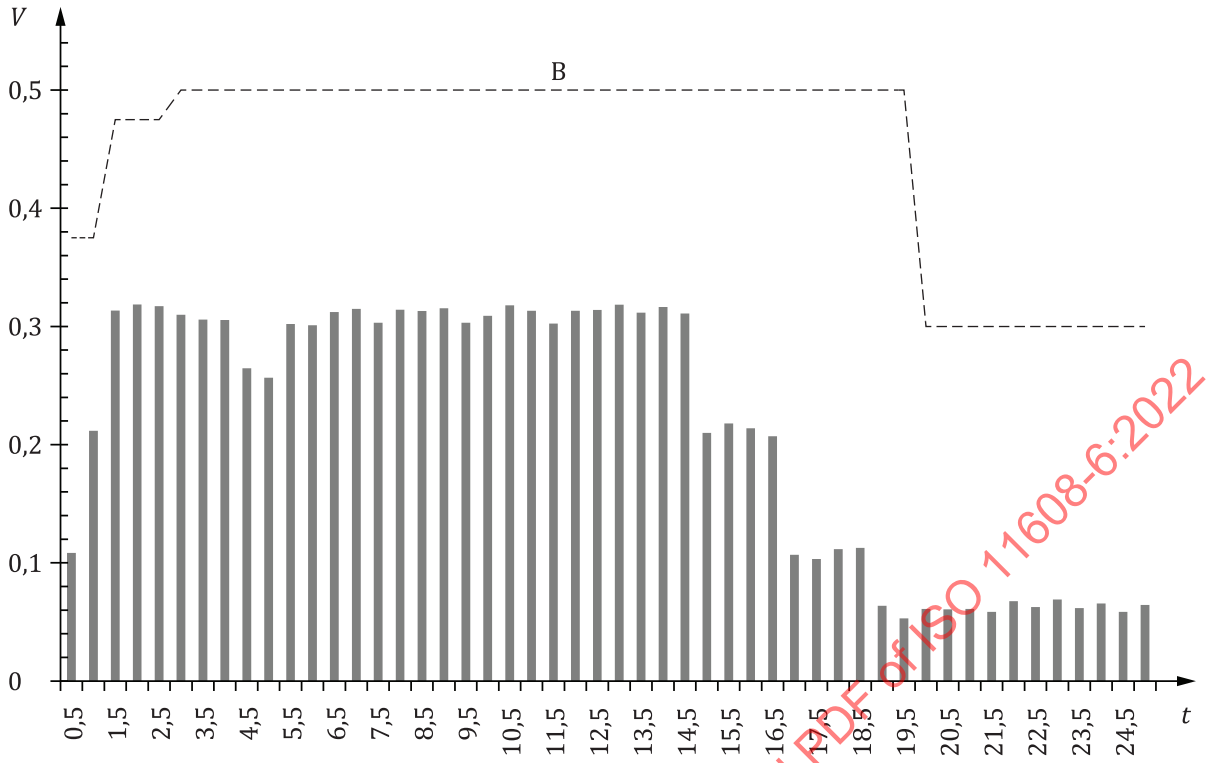
Key

V volume (in ml)

t time (in minutes)

A upper limit of dose volume at any measurement point (here shown as a constant with time)

Figure B.1 — Incremental volume against time with constant maximum limit



Key

V volume (in ml)

t time (in minutes)

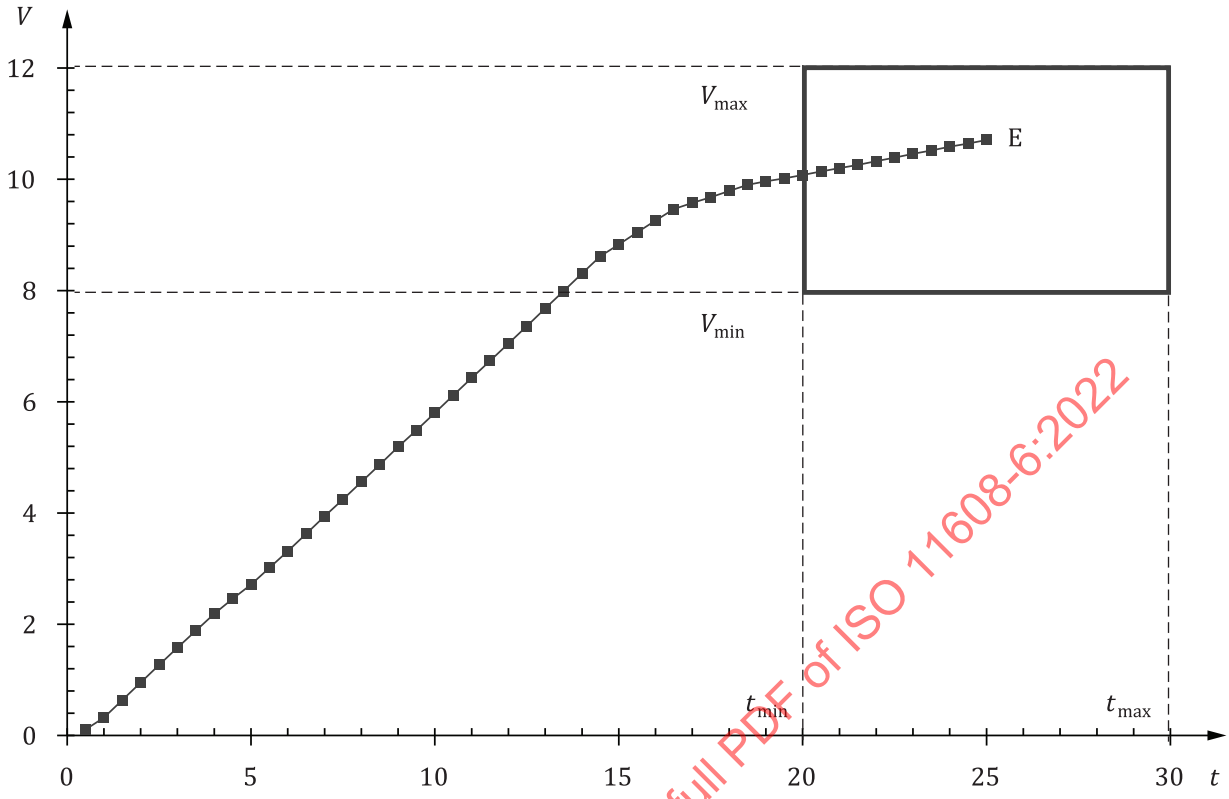
B upper limit of dose volume at any measurement point (here shown varying with time)

Figure B.2 — Incremental volume against time with varying maximum limit

B.4.2 Cumulative volume measurements against time – Line chart

The dose profile can be also be a measure of cumulative volume from the start of delivery, until the end of delivery, for example by using a method as described in B.4. Each data point represents the sum of incremental volumes up to that point in time. This type of dose profile is represented in Figure B.3.

This slope of this graph represents the average rate of delivery. The rate for any time interval can be determined by measuring the increase in delivered volume over the time period under analysis.



Key

V	volume (in ml)
t	time (in minutes)
E	end of delivery
V_{min}	minimum delivered dose
V_{max}	maximum delivered dose
t_{min}	minimum delivery time
t_{max}	maximum delivery time

Figure B.3 — Cumulative volume against time showing end of delivery

The end of delivery (point E) should be within the indicated rectangle to meet delivery volume and time specifications (where appropriate).

B.5 Setting specifications and limits for a dose delivery profile

In instances where the dose delivery profile is determined to be clinically relevant, acceptable limits for variability shall be established and the ability of the final OBDS to deliver the medicinal product consistent with the defined profile verified. It can also be helpful in other cases, such as when a large volume is delivered over a relatively long time.

Setting and meeting a specification limit, for example expressed as a maximum rate (e.g. not to exceed 1 ml/min), or as a maximum incremental volume (e.g. not to exceed 0,5 ml in any 30 s interval), can reduce or prevent patient discomfort from a fast injection. An example of a delivery profile that could result in patient discomfort could be a 10 ml dose with a nominal delivery time of 25 min that is delivered as 9,5 ml within the first minute and 0,5 ml for the remaining time.

It is also possible that a minimum specification limit for dose delivery profile is required. However, instances requiring a minimum dose delivery profile specification limit are likely to be rare since a minimum dose delivery volume will always be specified. When a minimum specification limit is required it should be specified and measured in a similar way to the maximum specification limit.

Figures B.1 and B.2 have two different types of specification for the same data. Figure B.1 shows a specification that remains constant throughout the delivery. In this graph the limit is that the delivered volume cannot exceed 0,5 ml. In Figure B.2, the maximum volume per time period varies, with a lower maximum volume at the start and at the end of delivery. Any plotted bar in the figure that crosses the maximum incremental volume line (whether constant limit A or varying limit B with time) indicates that the dose delivery profile is out of specification.

The graph in Figure B.3 shows the data represented as cumulative volume over time. Profile specification limits are not shown in this Figure. Specifying profile limits in relation to cumulative volume is complicated by the need to consider both the volume delivered up to any time point (the cumulative volume) and the difference in delivered volume between time points (the incremental volume), which means that a single line cannot describe the profile limit on the chart; the profile limit would need to be described considering both volume at any time (which would be represented by a line or lines offset from the nominal profile) and the rate of delivery (which would be represented by the gradient of the cumulative volume/time plot at any point). It is for this reason that the recommendation is to set limits using the approach of incremental volume against time.

It is important to note that for patient tolerability, a minimum volume or minimum rate is usually not required as it is likely that only large volumes over shorter time that can cause discomfort or Injection Site Reactions (ISRs).

B.6 Suggested method for measuring dose delivery profile

The manufacturer may use another suitable method.

a) Set up the OBDS on a fixture with the cannula positioned above a collecting vessel on a balance as shown in Figure B.4;

b) Zero the balance or record the initial mass;

c) Actuate the OBDS;

d) At each specified time interval (in the example above this would be 30 s), record the reading on the balance. This may be done using a data logger;

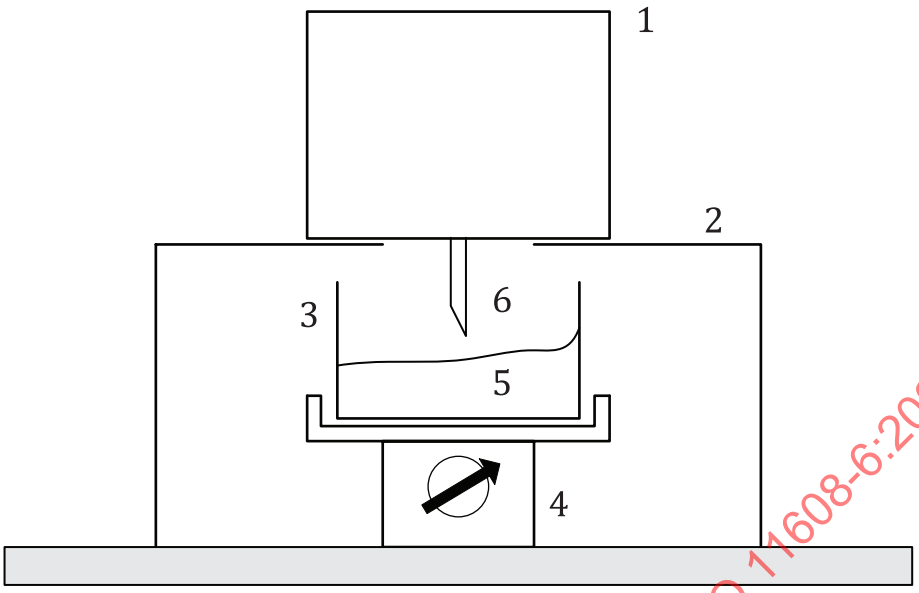
e) For each time interval calculate the incremental mass:

f) If total mass = m at time t, then incremental mass at time $t + 1$ is:

$$\Delta m_{t+1} = m_{t+1} - m_t$$

g) In order to determine the incremental volume, divide the incremental mass value by the density of the solution (or suspension);

h) To meet the dose delivery profile specification none of the incremental volumes may be more than the maximum dose delivery profile specification limit. If a minimum limit is specified, then none of the incremental volumes may be less than this limit.



Key

1 OBDS
2 fixture
3 collecting vessel
4 balance
5 liquid
6 cannula

Figure B.4 — Example of the dose delivery profile test set-up

A non-volatile liquid that is immiscible with and less dense than the delivered fluid may be placed in the collection vessel to prevent loss of the delivered fluid by evaporation. The non-volatile liquid will float on top of the delivered fluid and prevent evaporation.

It is possible to place fluid into the collecting vessel and arrange the OBDS such that the cannula is submerged in the fluid during delivery to prevent loss of delivered fluid by splashing in the collecting vessel. This may be the fluid being delivered, the non-volatile protection liquid described in the above paragraph or any other suitable liquid.

Annex C
(informative)

In vitro methods in relation to needle/cannula displacement

C.1 Background

The needle or a soft cannula of an OBDS forms the final delivery conduit for medication to reach the intended patient tissue. This annex outlines a number of the issues relevant to determining, measuring or recording the correct and consistent positioning of the tip of the needle or a soft cannula that require consideration by the manufacturer.

C.2 Discussion

Very little available or relevant predicate material describing test methods has been found in standards from other products or OBDSs with similar or equivalent features or functions.

Means to measure insertion depth at the time of placement and at the end of delivery can be identified (for both in-vivo and in vitro test purposes), and could include ultrasound and X-ray.

The fundamental issue of concern is that the tip of the needle/cannula should remain in a known and correct position in the intended patient tissue during the period in use, and should not be adversely affected by patient activity. The OBDS instructions for use should stipulate what range of patient activity falls within scope.

The requirements of the tip placement should reflect the intended tissue type and location, as well as the duration over which the drug is to be delivered. This duration, in turn, will vary based on the OBDS/drug combination and will depend upon a number of factors, in large part dictated by patient tolerance. Tolerance will be influenced by factors such as OBDS configuration, drug viscosity, pH, osmolarity and temperature of the drug.

Other characteristics requiring consideration are likely to include potential hazards such as movement, adhesive strength/skin adhesion, bending, and damage during insertion. Risk control measures that can be pertinent in eliminating or reducing such risks should form a part of the overall risk management plan. Risk analysis may include knowledge and experience of the particular OBDS or other OBDSs sharing similar features, catheters or adhesive systems, in addition to field data and clinical evidence.