
Pen-injectors for medical use —

Part 1:

**Pen-injectors — Requirements and test
methods**

Stylos-injecteurs à usage médical —

Partie 1: Stylos-injecteurs — Exigences et méthodes d'essai

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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.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 3.

Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

Attention is drawn to the possibility that some of the elements of this part of ISO 11608 may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

International Standard ISO 11608-1 was prepared by Technical Committee ISO/TC 84, *Medical devices for injections*.

ISO 11608 consists of the following parts, under the general title *Pen-injectors for medical use*:

- *Part 1: Pen-injectors — Requirements and test methods*
- *Part 2: Needles — Requirements and test methods*
- *Part 3: Finished cartridges — Requirements and test methods*

Annex A of this part of ISO 11608 is for information only.

Introduction

This part of ISO 11608 covers pen-injectors primarily intended for human use. It provides performance requirements regarding essential aspects, so that variations of design are not unnecessarily restricted.

The devices described in this part of ISO 11608 are designed to be used with devices described in ISO 11608-2 and ISO 11608-3.

It is recognized that interchangeability of the components (pen-injector, needle and cartridge) is desirable for some medicinal products and to be avoided for other medicinal products, and that future design may change the current concepts. Therefore, ISO 11608-2 and ISO 11608-3 encourage interchangeability by establishing certain specific requirements for interchangeable needles (Type A) and interchangeable cartridges (Type A) respectively.

Performance requirements are imposed on both Type A (interchangeable) and non-Type A needles and cartridges. Additional dimensional requirements are imposed on Type A needles and cartridges and hereby indirectly on pen-injectors intended for either Type A needles and/or Type A cartridges.

Information as to whether the components are interchangeable (Type A) or not should be given on the unit container.

The sampling plans for inspection selected for this part of ISO 11608 are intended to verify, at a high confidence level, the manufacturer's ability to manufacture one "lot" of pen-injectors that conforms to the critical product attributes. The sampling plans for inspection do not replace the more general manufacturing quality systems that appear in standards on quality systems, e.g. the ISO 9000 series.

Materials to be used for the construction are not specified, as their selection to some extent will depend upon the design, the intended use and the process of manufacture by individual manufacturers. All materials should be resistant to the medicinal product intended to be injected with the pen-injector.

In some countries national regulations exist, and their requirements may supersede or complement this part of ISO 11608.

Pen-injectors for medical use —

Part 1:

Pen-injectors — Requirements and test methods

1 Scope

This part of ISO 11608 specifies requirements and test methods for pen-injectors intended to be used with needles and with replaceable or non-replaceable prefilled cartridges.

This part of ISO 11608 is also applicable to pen-injectors which are not electrically driven, but are equipped with electronic components.

This part of ISO 11608 is not applicable to high-pressure injectors and electrically driven injectors.

2 Normative references

The following normative documents contain provisions which, through reference in this text, constitute provisions of this part of ISO 11608. For dated references, subsequent amendments to, or revisions of, any of these publications do not apply. However, parties to agreements based on this part of ISO 11608 are encouraged to investigate the possibility of applying the most recent editions of the normative documents indicated below. For undated references, the latest edition of the normative document referred to applies. Members of ISO and IEC maintain registers of currently valid International Standards.

ISO 11608-2:2000, *Pen-injectors for medical use — Part 2: Needles — Requirements and test methods.*

ISO 11608-3:2000, *Pen-injectors for medical use — Part 3: Finished cartridges — Requirements and test methods.*

IEC 60068-2-6:1995, *Environmental testing — Part 2: Tests. Test Fc: Vibration (sinusoidal).*

IEC 60068-2-6:1995, *Corr. 1.*

IEC 60068-2-30:1980, *Environmental testing — Part 2: Tests. Test Db and guidance: Damp heat, cyclic (12 + 12-hour cycle).*

IEC 60068-2-30, *Amendment No. 1:1985.*

IEC 61000-4-2:1999, *Electromagnetic compatibility (EMC) — Part 4-2: Testing and measurement techniques — Electrostatic discharge immunity test.*

IEC 61000-4-3:1998, *Electromagnetic compatibility (EMC) — Part 4-3: Testing and measurement techniques — Radiated, radio-frequency, electromagnetic field immunity test.*

3 Terms and definitions

For the purposes of this part of ISO 11608, the following terms and definitions apply.

The nomenclature of some components of pen-injectors is illustrated in Figure 1.

3.1

pen-injector

medical device intended for parenteral administration by injection of medicinal products from a multidose cartridge

NOTE The doses may be pre-set by manufacturer or user.

3.2

connector

mechanical arrangement allowing the connection between the needle and the cartridge

3.3

cartridge

primary container for the medicinal product

3.4

injection mechanism

mechanism which performs the parenteral injection of the pre-set dose

3.5

release mechanism

mechanism which initiates the parenteral injection of the pre-set dose

3.6

injection stroke

that portion of a parenteral injection involving movement of the injection mechanism following initiation by the release mechanism

NOTE It does not include the subsequent relaxation of the system components required for the complete injection of the pre-set dose.

3.7

mechanism holder

part of the body of the injector containing the injection mechanisms

3.8

selector

mechanism which allows pre-setting of a dose

3.9

increment

smallest possible difference to be selected between two dose amounts

3.10

indicator

means by which the amount of pre-set dose is shown

3.11

residual scale

graduated scale which indicates the remainder of medicinal product in the cartridge

3.12

dose accuracy

accuracy with which the pen-injector delivers a pre-set dose of medicinal products

3.13

cap

part of the pen-injector intended to protect the system

3.14**pre-setting**

procedure by which individual amounts of medicinal product can be selected for injection by the user

3.15**unit container**

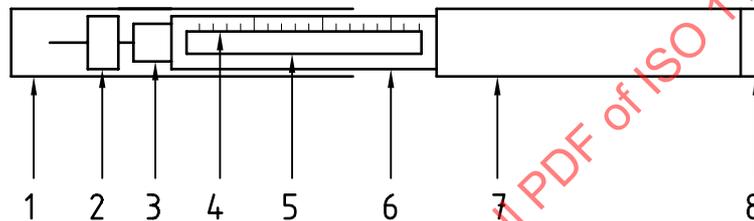
package intended for customer use

3.16**Type A**

classification of needles and cartridges for pen-injectors which fulfil certain specific requirements providing interchangeability

3.17**non-Type A**

classification of needles and cartridges which are not classified as Type A

**Key**

- 1 Cap
- 2 Injection system
- 3 Connector
- 4 Residual scale
- 5 Window
- 6 Cartridge holder
- 7 Mechanism holder
- 8 Release mechanism

Figure 1 — Schematic presentation of a pen-injector

4 Symbols and abbreviations

V_{set} One of the three pre-set doses (expressed as a volume, in millilitres) used in determining the dose accuracy for a given pen-injector. V_{set} is defined as one of the following:

- a) minimum dose ($V_{\text{set}} = V_{\text{min}}$) (specified in the instructions for use);
- b) maximum dose ($V_{\text{set}} = V_{\text{max}}$) (specified in the instructions for use);
- c) midpoint dose ($V_{\text{set}} = V_{\text{mid}}$), where V_{mid} is defined as the injector setting closest to $(V_{\text{min}} + V_{\text{max}})/2$.

NOTE Recommended doses as specified in the instruction for use may differ from those doses that can be set.

V_{meas} The volumetric measurement value for a given V_{set}

G_{meas} The gravimetric measurement value for a given V_{set}

- ρ Density, expressed in grams per millilitre
- p Probability content
- Y Number of pens required for a given test
- R Number of replicates required for a given test. A replicate is a random sequence of V_{\min} , V_{mid} , and V_{\max} . There are six possible replicates.
- n Number of measurements (V_{meas}) to be made for each V_{set}
- \bar{x} The sample mean; when based on a random sample, an estimate of the true mean:

$$\bar{x} = \sum V_{\text{meas}} / n$$

- s The sample standard deviation; when based on a random sample, an estimate of the true standard deviation:

$$s = \left[\sum (V_{\text{meas}} - \bar{x})^2 / (n - 1) \right]^{1/2}$$

- k Tolerance Limit Factor, determined from the confidence level (95 %), probability content (p) and the number of accuracy measurements (n) conducted at each dose setting
- α Absolute error (millilitres) used to define the upper and lower specification limits for a pre-set dose in absolute terms
- β Relative error (%) used to define the upper and lower specification limits for a pre-set dose in relative terms
- TP The transition point volume (millilitres) at which the definition of the upper and lower specification limits for V_{set} changes from absolute terms to relative terms:
- $$TP = (100 \times \alpha) / \beta$$
- U Upper specification limit for a given V_{set}
- L Lower specification limit for a given V_{set}

5 General requirements

When the pen-injector is ready for injection, the cartridge holder shall allow visibility of the deliverable volume. It shall be possible to determine whether sufficient medicinal product remains in order to administer the maximum pre-settable dose.

The pen-injector shall be designed such that it is able to deliver the labelled volume from the cartridge for which it is designed.

The pen-injector shall be designed such that the last dose delivered from a cartridge satisfies requirements for dose accuracy.

The pen-injector shall indicate the pre-set dose.

The pen-injector shall indicate, at least by visual means, that it is ready for injection. There shall be an indication of the pre-setting procedure by tactile or audible means, or both.

The state of the pen-injector, when ready to deliver a dose, shall be different to its state when the dose has been delivered. The difference shall be visible.

The pen-injector shall indicate, by visual, audible or tactile means or any combination of these, that the injection stroke has been completed.

If the pen-injector is designed for variable doses, it shall be so designed that it is impossible to deliver a second dose after delivery of the first dose without a second pre-setting.

The pen-injector shall be so designed that it:

- does not allow a larger dose to be pre-set than is left in the cartridge; or
- does not allow dose delivery if the pre-set amount exceeds the amount of medicinal product left in the cartridge; or
- indicates the amount of medicinal product delivered; or
- indicates the amount of medicinal product not delivered of the pre-set dose.

The pen-injector shall be designed to function with a needle fulfilling the specifications of ISO 11608-2.

If the pen-injector is designed to function with a single-compartment cartridge, it shall be designed to function with a cartridge fulfilling the specifications of ISO 11608-3.

6 Test conditions

6.1 Standard atmosphere

Unless otherwise specified, measurements shall be performed in the following atmosphere:

- temperature: from 18 °C to 28 °C;
- relative humidity: from 25 % RH to 75 % RH;

after having been subjected to storage for at least 4 h in this atmosphere.

6.2 Cool atmosphere

The assembled pen-injector with the cartridge and needle is placed in a test chamber for at least 4 h in the following cool atmosphere:

- temperature: (5 ± 3) °C.

6.3 Hot atmosphere

The assembled pen-injector with the cartridge and needle is placed in a test chamber for at least 4 h in the following hot atmosphere:

- temperature: (40 ± 2) °C;
- relative humidity: (50 ± 10) % RH.

7 Preconditioning of pen-injectors

7.1 Preconditioning in dry heat atmosphere

The pen-injector without the cartridge and needle is placed in a test chamber for at least 96 h in the following hot atmosphere:

- temperature: (70 ± 2) °C;
- relative humidity: (50 ± 10) % RH.

7.2 Preconditioning in cold storage atmosphere

The pen-injector without the cartridge and needle is placed in a test chamber for at least 96 h in the following cold atmosphere:

- temperature: (-40 ± 3) °C.

7.3 Preconditioning in cyclical atmosphere

The pen-injector with the cartridge and without the needle is placed in a test chamber. Conditioning in accordance with IEC 60068-2-30 is carried out as follows:

- variant 1 (see IEC 60068-2-30, Figure 2a);
- upper temperature: (55 ± 2) °C; and
- 6 cycles.

NOTE The relevant clauses of IEC 60068-2-30:1980 are: clauses 3, 6 and 8.

7.4 Preconditioning by free fall

Prepare the pen-injector according to the instructions for use with a new cartridge and proceed as follows:

- a) Pen-injectors with replaceable cartridges
 - 1) Expel the air.
 - 2) Take off the needle and put on the cap.
 - 3) Drop each pen-injector three times by free fall from a height of 1 000 mm onto the test surface (see 8.3), once horizontally and twice vertically, the pen-injector being rotated 180° between the two vertical drops. Care shall be taken that the pen-injector is released in a non-turbulent way.
 - 4) If a cartridge breaks such that it is obvious to the user, replace the cartridge and continue until all three drops have been performed.
- b) Pen-injectors with non-replaceable cartridges
 - 1) Expel the air.
 - 2) Take off the needle and put on the cap.
 - 3) Drop the pen-injectors by free fall from a height of 1 000 mm onto the test surface (see 8.3) in accordance with i), ii) and iii), as follows:

i) Horizontal

Drop a minimum of 10 new pen-injectors in a non-turbulent way. If a cartridge breaks such that it is obvious to the user, exclude the pen-injector from further testing.

ii) Vertical A

Drop a minimum of 10 new pen-injectors in a non-turbulent way. If a cartridge breaks such that it is obvious to the user, exclude the pen-injector from further testing.

iii) Vertical B [180° from orientation ii)]

Drop a minimum of 10 new pen-injectors in a non-turbulent way. If a cartridge breaks such that it is obvious to the user, exclude the pen-injector from further testing.

7.5 Preconditioning by vibration for pen-injectors with electronic components

Vibrate the pen-injector with its cartridge and needle in each of three axes in accordance with IEC 60068-2-6 and Table 1.

Table 1 — Vibration amplitudes with lower cross-over frequency: IEC 60068-2-6:1995, Table IV and Figure 1

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 The sweep speed shall be 1 octave per minute.

8 Reagent and apparatus

8.1 Test liquid, i.e. the original medicinal product intended to be injected by the pen-injector or a liquid which gives the same results.

8.2 Balance, with a maximum tolerance of 1 % of the minimum dose delivery.

8.3 Test surface, smooth, hard, rigid steel of 3 mm thickness backed by wood of between 10 mm and 19 mm thickness.

8.4 Needle connector for connecting the needle to a tube.

9 Determination of dose accuracy

9.1 Dose accuracy

9.1.1 General

Dose accuracy is determined by selecting and testing a variable number of pen-injectors. The number of pen-injectors depends upon the cartridge and accuracy requirements for a given test. Assuming that the accuracy measurements are normally distributed and that each measurement is independent, the following method enables accuracy measurements to be used as the basis for determining a statistical tolerance interval for three dose settings (the minimum, midpoint and maximum dose settings for a given pen-injector), i.e. an interval such that there is a fixed probability (confidence level) that the interval will contain at least a proportion (p , probability content)

of the true population from which the sample is taken. The statistical tolerance interval is two-sided, and the limits of the interval are called “statistical tolerance limits” or “natural limits of the process”.

To pass the dose accuracy requirement, there shall be a 95 % confidence that at least p of all doses delivered will fall within the proposed upper and lower specification limits for the three dose settings.

The two-sided statistical tolerance interval is calculated using the mean (\bar{x}) plus or minus the standard deviation (s) multiplied by a tolerance limit factor (k):

$$\bar{x} \pm k \cdot s$$

where

\bar{x} is the mean of the sample;

k is the tolerance limit factor;

s is the standard deviation of the sample.

The factor is determined based upon the confidence level (95 %), probability content (p), and the number of measurements (n) taken for each of the three dose settings. ISO 3207:1975^[1], Table 8, lists the tolerance limit factors for the construction of two-sided statistical tolerance intervals when the true population mean and standard deviation are not known. Annex A contains a more comprehensive two-sided tolerance limit for the 95 % confidence level.

9.1.2 Accuracy assessment (expressed in millilitres)

If $V_{\text{set}} \leq TP$, then:

$$U = V_{\text{set}} + \alpha;$$

$$L = V_{\text{set}} - \alpha.$$

If $V_{\text{set}} > TP$, then:

$$U = V_{\text{set}} + (\beta \cdot V_{\text{set}}) / 100;$$

$$L = V_{\text{set}} - (\beta \cdot V_{\text{set}}) / 100.$$

A pen-injector population's accuracy satisfies the requirements when, for a given V_{set} , the following are fulfilled:

$$\bar{x} + (k \cdot s) \leq U; \text{ and}$$

$$\bar{x} - (k \cdot s) \geq L.$$

9.1.3 Example of accuracy limit calculation

In the following an example of calculation (volumes expressed as millilitres) is given for a single-compartment cartridge:

If V_{set} :

$$V_{\text{min}} = 0,02 \text{ ml};$$

$$V_{\text{mid}} = 0,16 \text{ ml};$$

$$V_{\text{max}} = 0,30 \text{ ml};$$

and:

$$\alpha = 0,01 \text{ ml};$$

$$\beta = 5 \%;$$

then:

$$TP = (100 \times 0,01 \text{ ml})/5 = 0,20 \text{ ml};$$

$$\text{For } V_{\min} \leq TP: \quad U = (0,02 + 0,01) \text{ ml} = 0,030 \text{ ml};$$

$$L = (0,02 - 0,01) \text{ ml} = 0,010 \text{ ml};$$

$$\text{For } V_{\text{mid}} \leq TP: \quad U = (0,16 + 0,01) \text{ ml} = 0,170 \text{ ml};$$

$$L = (0,16 - 0,01) \text{ ml} = 0,150 \text{ ml};$$

$$\text{For } V_{\max} > TP: \quad U = 0,30 \text{ ml} + (5 \times 0,30 \text{ ml})/100 = 0,315 \text{ ml};$$

$$L = 0,30 \text{ ml} - (5 \times 0,30 \text{ ml})/100 = 0,285 \text{ ml}.$$

9.1.4 Procedure

9.1.4.1 General

All doses (V_{set}) delivered are recorded gravimetrically (G_{meas} , expressed in grams). These recordings are converted to volumes (V_{meas}) by using the density (ρ , expressed in grams per millilitre) for the test fluid. The following equation can be used to convert gravimetric measurements to volumetric:

$$V_{\text{meas}} = G_{\text{meas}} / \rho$$

9.1.4.2 Accuracy requirements

Using the confidence level of 0,950 (95 %) and the minimum test requirements presented in Table 2 and in 9.1.2, the two-sided statistical tolerance interval for a given test and V_{set} can be calculated. See clause 4 for the meaning of symbols.

Table 2 — Minimum test requirements for pen-injectors

Test	Subclause	R	Y ^a	n	k ^b	Replaceable with electronics	Replaceable without electronics	Non-replaceable
Series A (p = 0,975)	9.2.2	4	15	60	2,670	x	x	x
	9.2.4					x	x	x ^c
	9.2.5					x	x	x ^d
Series B (p = 0,950)	9.2.3	4	5	20	2,760	x	x	—
	10.1					x	x	—
	10.2					x	—	—
	10.3					x	x	x
	11.2					x	—	—
	11.3					x	—	—

a Pen-injectors with nonreplaceable cartridges may require additional pen-injectors to fulfil the replicate (R) and free-fall (refer to 10.3) requirements.

b k-values are obtainable from ISO 3207 or annex A.

c Pen-injectors with a lower acceptable storage temperature shall be subjected to the test at the acceptable temperature.

d Pen-injectors with a higher acceptable storage temperature shall be subjected to the test at the acceptable temperature.

9.1.4.3 Preparation and operation of pen-injectors

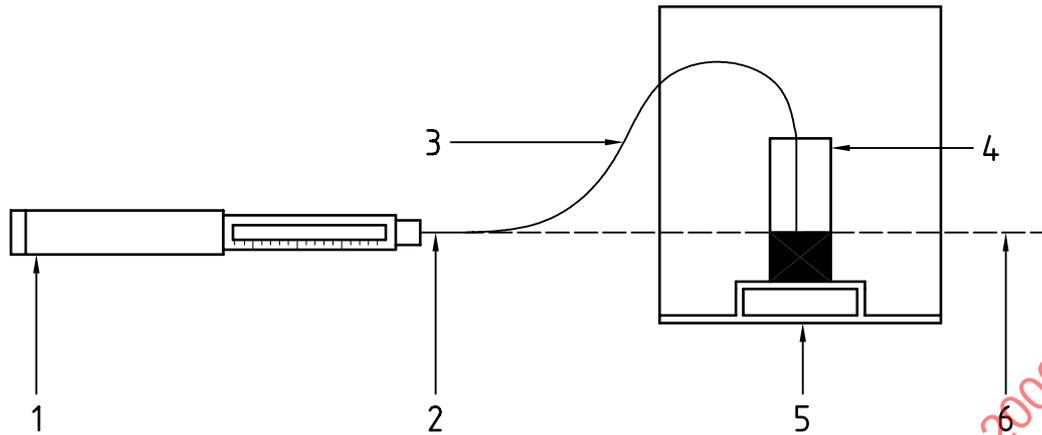
A test system as shown in Figure 2 can be used. Other types of test system can be used when the accuracy obtainable with the system shown in Figure 2 can be obtained. The repeatability and reproducibility (gauge R&R) of the test apparatus should be no greater than 20% of the allowed tolerance band for any given set of measurements.

Prepare the pen-injector in accordance with the instructions for use.

Carry out the test so that the operation of the pen-injector simulates that described in the instructions for use.

Fill the system with the test liquid and remove all bubbles. The weighing glass shall contain enough test liquid for the tip of the needle tube to be below the surface.

Connect the pen-injector with the system so that the injection is made through the original needle into the rigid tube.

**Key**

- 1 Pen-injector
- 2 Needle connector
- 3 Needle tube
- 4 Weighing glass
- 5 Balance with a maximum tolerance of 1 % of minimum dose
- 6 Level of test liquid

Figure 2 — Example of test system (schematic)

Operate the pen-injector manually or automatically.

Determine the dose delivered (G_{meas}) by reading the balance 5 s (or as specified in the instructions for use) after completion of the injection stroke.

When the maximum number of operations have been reached for a pen-injector with replaceable cartridge and with a built-in limited number of operations, replace the pen-injector.

9.1.4.4 Random settings

For a given test, dose accuracy is 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):

$R_1: V_{\text{min}}, V_{\text{mid}}, V_{\text{max}};$

$R_2: V_{\text{min}}, V_{\text{max}}, V_{\text{mid}};$

$R_3: V_{\text{mid}}, V_{\text{min}}, V_{\text{max}};$

$R_4: V_{\text{mid}}, V_{\text{max}}, V_{\text{min}};$

$R_5: V_{\text{max}}, V_{\text{min}}, V_{\text{mid}};$

$R_6: V_{\text{max}}, V_{\text{mid}}, V_{\text{min}}.$

Depending upon the number of replicates required, cartridge size and the three dose levels, a given pen-injector will require a variable number of cartridges. Therefore, some replicates may be expelled (partial injection sequences) from two cartridges.

EXAMPLE

- If: 1) replicates: $R = 3$;
- 2) dose levels: $V_{\min} = 0,01 \text{ ml}$; $V_{\text{mid}} = 0,30 \text{ ml}$; $V_{\max} = 0,60 \text{ ml}$;
- 3) cartridge size: $1,5 \text{ ml}$;
- 4) replicates sequence: R_1, R_4, R_3 ;
- 5) total doses: 9 ;

then the cartridge use, replicate order and V_{set} dose sequence (expressed in millilitres) for each pen-injector tested is shown in Table 3.

Table 3 — Example of random dose sequence

Random sequence	R_1	R_4	R_3
Dose levels, ml	0,01 – 0,30 – 0,60	0,30 – 0,60 – 0,01	0,30 – 0,01 – 0,60
1,5 ml – Cartridge No.	1	2	3

9.2 Dose accuracy requirements

9.2.1 General

The dose accuracy shall be in accordance with the specifications in Table 4.

Table 4 — Specification limits for dose accuracy of pen-injectors

Type of pen-injector	Absolute error of pre-set dose α	Relative error of pre-set dose β	Transition point TP
With single-compartment cartridge	0,01 ml	5 %	0,2 ml
With multiple-compartment cartridge	0,01 ml	10 %	0,1 ml

9.2.2 Dose accuracy when subjected to standard, cool and hot atmospheres

Determine the dose accuracy of an appropriate number of new pen-injectors in accordance with 9.1, under the conditions specified in 6.1. Repeat the dose accuracy test on the same pen-injectors with replaceable cartridges and on other pen-injectors with non-replaceable cartridges as appropriate under the conditions of 6.2 and again under the conditions of 6.3.

9.2.3 Dose accuracy and lifetime test of pen-injectors with replaceable cartridges after delivery of claimed lifetime doses

Operate five pen-injectors previously used for determining the dose accuracy in accordance with 9.2.2, simulating manual use in accordance with the instructions for use, as follows:

- a) remove the cap permanently if it has no influence on the safety of the pen;
- b) insert a cartridge;
- c) attach a needle;
- d) prepare the pen-injector for injection;
- e) expel a dose of V_{mid} or 0,2 ml, whichever is the smallest amount;
- f) repeat c) to e) until the cartridge is empty;
- g) repeat b) to f) until 1,5 times the number of injection strokes of the lifetime (in accordance with the manufacturers product file) is reached.

If the pen-injector is designed to stop working after a limited time or number of operations, the total number of operations shall be adopted for this test.

Determine the dose accuracy of the five pen-injectors in accordance with the specifications in 9.1.

9.2.4 Dose accuracy after being subjected to dry heat storage preconditioning

Subject an appropriate number, see 9.1, of new pen-injectors to the preconditioning in accordance with 7.1.

None of the pen-injectors shall have visible defects after removal from the hot storage atmosphere when inspected in accordance with clause 12.

Return the pen-injectors to the standard conditions and determine the dose accuracy of the pen-injectors in accordance with 9.1.

Pen-injectors with a lower acceptable storage temperature, e.g. pen-injectors with non-replaceable cartridges, shall be subjected to preconditioning at the acceptable temperature, and this acceptable temperature shall be stated in the instructions for use.

9.2.5 Dose accuracy after being subjected to cold storage preconditioning

Subject an appropriate number, see 9.1, of new pen-injectors to the preconditioning in accordance with 7.2.

None of the pen-injectors shall have visible defects after removal from the cold storage atmosphere when inspected in accordance with clause 12.

Return the pen-injectors to the standard conditions and determine the dose accuracy of the pen-injectors in accordance with 9.1.

Pen-injectors with a higher acceptable storage temperature, e.g. pen-injectors with non-replaceable cartridges, shall be subjected to preconditioning at the acceptable temperature, and this acceptable temperature shall be stated in the instructions for use.

10 Freedom from defects

10.1 Freedom from defects after being subjected to cyclical preconditioning

Subject an appropriate number, see 9.1, of new pen-injectors to the preconditioning in accordance with 7.3.

None of the pen-injectors shall have visible defects after removal from the preconditioning atmosphere when inspected in accordance with clause 12.

None of the pen-injectors shall have functional defects after removal from the preconditioning atmosphere when inspected in accordance with clause 13.

Pen-injectors with a non-replaceable cartridge inserted shall not be required to fulfil the requirements of this sub-clause.

10.2 Freedom from defects after being subjected to vibration

Subject an appropriate number, see 9.1, of new pen-injectors with electronic components to the preconditioning in accordance with 7.5.

None of the pen-injectors shall have visible defects after vibration when inspected in accordance with clause 12.

None of the pen-injectors shall have functional defects after vibration when inspected in accordance with clause 13.

10.3 Freedom from defects after being subjected to free fall

Subject an appropriate number, see 9.1, of new pen-injectors to the preconditioning in accordance with 7.4.

None of the pen-injectors shall have visible defects after the free fall when inspected in accordance with clause 12.

None of the pen-injectors shall have functional defects after the free fall when inspected in accordance with clause 13.

11 Determination of electromagnetic compatibility

11.1 Electromagnetic compatibility (EMC)

11.1.1 General

NOTE The tests specified in 11.1.2 and 11.1.3 are based on the requirements given in the collateral standard IEC 60601-1-2:1993 for EMC. In this part of ISO 11608, EMC references are given to the IEC 61000-4-1:1992 standards (IEC 61000-4-2:1995 and IEC 61000-4-3:1995 in particular). The range of the sweep in this part of ISO 11608 covers all frequencies of mobile communication systems.

The requirements given in 11.2 and 11.3 are requirements substituting those specified in IEC 60601-1-2, as the latter standard covers requirements for electromedical appliances in general only, and it does not address specific devices such as pen-injectors.

11.1.2 Exposure to electrostatic discharge

Place the pen-injector with the cartridge on a metal reference plane as specified in IEC 61000-4-2. Apply contact discharges of ± 2 kV, ± 4 kV and ± 8 kV to conductive accessible parts and coupling planes. Apply air discharges of ± 8 kV, ± 10 kV, ± 12 kV and ± 15 kV to nonconductive accessible parts. Apply ten discharges at each level and polarity with a time interval of 1 s between the individual discharges.

11.1.3 Exposure to radiated fields (RF)

Perform the test in accordance with IEC 61000-4-3:1995, in which TEM cells or GTEM cells may be used as described in annex D. As stated in IEC 61000-4-3, the requirement for field uniformity shall be fulfilled in the area corresponding to the unit under test.

The test level shall be 10 V/m (unmodulated carrier) in the frequency range of 26 MHz to 2 000 MHz. The test signal shall be AM-modulated with 1 kHz sinusoidal and to a modulation depth of 80 %. Perform the test in each of the three axes of the pen-injector.

11.2 Electrostatic discharge

Visually inspect the performance (e.g. stored data, settings, dose or indications) of five new pen-injectors with electronic components.

The pen-injectors shall fulfil the following requirements:

- a) none of the pen-injectors shall exhibit visible defects after each and all the required electrostatic discharges when tested in accordance with 11.1.2;
- b) the performance of the pen-injector (e.g. stored data, settings, dose or indications) shall not change as a result of the application of the test. None of the pen-injectors shall have functional defects, in accordance with clause 13.

11.3 Radiated radio frequency (RF) fields

Visually inspect the performance (e.g. stored data, settings, dose or indications) of five new pen-injectors with electronic components.

The pen-injectors shall fulfil the following requirements:

- a) none of the pen-injectors shall exhibit erroneous indications during the radio frequency sweep when tested in accordance with 11.1.3;
- b) after the application of the radio frequency sweep, the performance of the pen-injector shall be inspected. The performance of the pen-injector (e.g. stored data, settings, dose or indications) shall not change as a result of the application of the test. None of the pen-injectors shall have functional defects, in accordance with clause 13.

12 Visual inspection

Inspect the pen-injector for significant defects under normal or corrected-to-normal vision. Defects in electronic parts leading to nonfunctioning are permitted if the nonfunctioning is obvious to the user.

The inspection should in particular include checking for significant defects such as:

- displaced parts;
- non-intact marking;
- cracks in the body and/or component of the pen-injector; and
- the fixation between the different parts of the body of the pen-injector.

13 Functional inspection

13.1 Replaceable cartridge

Check the cartridge. If broken to the extent that is obvious to the user, replace the cartridge and test for dose accuracy.

13.2 Nonreplaceable cartridge

Check the cartridge. If broken to the extent that is obvious to the user, exclude the pen-injector from further testing.

A minimum of ten pen-injectors are required to withstand the free-fall test and to be used for dose accuracy testing; otherwise the test is considered to have failed.

13.3 Accuracy

The accuracy of the pen-injector shall be within the accuracy required in clause 9 when tested in accordance with test series B specified in Table 2.

14 Test report

Each report of the testing performed in accordance with this part of ISO 11608 shall include at least the following information:

- a) a reference to this part of ISO 11608;
- b) identification of the pen-injector tested;
- c) identification of the test system used;
- d) identification of the test liquid used;
- e) the test results;
- f) details of any deviation from this part of ISO 11608, e.g. specification of test system if the test system illustrated in Figure 2 has not been used;
- g) the name and address of the test facility;
- h) the date of test;
- i) if the pen-injector is designed to deliver a fixed dose, the minimum and the maximum doses shall be stated, if the doses expelled for testing are not identical with the fixed dose.

15 Information supplied by the manufacturer

15.1 General

The pen-injector shall be accompanied by sufficient information to use it safely, taking into account the training and knowledge of the potential users, and to identify the manufacturer.

Instructions for use shall be included in the unit container.

15.2 Marking

15.2.1 General

Any marking on the pen-injector that is essential for the safe use of the device shall be visible, easily legible and indelible after being subjected to the preconditioning specified in 7.3. Any marking on the unit container that is essential for the safe use of the pen-injector shall be visible and legible. This shall be checked by visual inspection by normal, or corrected-to-normal, vision at environmental lighting condition of (215 ± 20) lx.

15.2.2 Marking on the pen-injector

The marking on the pen-injector shall at least comprise the following particulars:

- a) name or trade name of the manufacturer;

NOTE A trademark or logo may be sufficient to identify the manufacturer.
- b) details necessary for the user to identify the pen-injector;
- c) batch code, the lot number or the serial number preceded by an appropriate symbol.

15.2.3 Marking on the unit container

The marking on the unit container shall comprise at least the following particulars:

- a) name and address of the manufacturer;
- b) details necessary for the user to identify the pen-injector;
- c) content of the unit container;
- d) information on the type of medicinal product(s) intended to be injected by means of the pen-injector;
- e) batch code, lot number or the serial number preceded by an appropriate symbol;
- f) any special storage and/or handling conditions;
- g) expiry date, if any (year and month, expressed e.g. as CCYY-MM, example: 1996-12);
- h) if the pen-injector is intended to be used with Type A needles and/or cartridges in accordance with respectively ISO 11608-2 or ISO 11608-3, the unit container shall carry the text: "For use with TYPE A needles" and/or: "For use with TYPE A cartridges", including information on the medicinal product for which it is intended.

15.3 Instructions for use

The instructions for use shall contain information on at least the following particulars:

- a) the information required in 15.2, except that the information regarding expiry date, if any, lot number, batch code or serial number can be omitted;
- b) any warnings and/or precautions to be taken; e.g. that the pen-injector shall not be used for injections if it is obvious to the user that it does not function correctly;
- c) any risks associated with its normal use, e.g.:
 - 1) in the case of pen-injectors with pre-fixed dosages, that they shall only be used by persons able to calculate the number of activations correctly when injection is performed;

- 2) that pen-injectors with electronic components shall not be used close to electromagnetic radiant areas, e.g. close to mobile telephones in use, if the pen-injectors are not specially designed to be used in such areas;
- d) sufficient details of its characteristics to identify the pen-injector and related equipment in order to obtain a safe combination;
- e) information on the appropriate process to allow re-use of the pen-injector, including cartridge replacement, cleaning and disinfection;
- f) details on any preparation needed before the pen-injector can be used, e.g.:
- 1) the need to prime before each injection;
 - 2) how to assemble/disassemble the product, replace the cartridge and attach the needle;
- g) description of the method of use, e.g. setting the dose, reading the scales, mixing a suspension, removing excess air, injection procedure as step-by-step operations;
- h) time to wait before removing the needle from the injection site;
- i) dose-setting range;
- j) if acceptable storage temperatures are other than those specified in 7.1 and 7.2 (+ 70 °C and – 40 °C), the acceptable temperature range for storage of the pen-injector without medicinal product;
- k) procedure for delivering a dose, when the remaining volume of liquid in the cartridge is less than the volume to be injected;
- l) any special storage requirements;
- m) type of replaceable batteries and their number, if used;
- n) description of special features;
- o) whether the pen-injector is designed so that it:
- does not allow a larger dose to be pre-set than is left in the cartridge; or
 - does not allow dose delivery if the pre-set exceeds the amount of medicinal product left in the cartridge; or
 - indicates the amount of medicinal product delivered; or
 - indicates the amount of medicinal product not delivered of the pre-set dose.
- p) if Type A needles and/or cartridges in accordance with ISO 11608-2 or ISO 11608-3 are intended to be used, it shall be stated that needles and/or cartridges marked with TYPE A shall be used;
- if non-Type A needles and/or cartridges are intended to be used with the pen-injector, it shall be stated which identified needles and cartridges are to be used;
- q) details allowing the medical staff to brief the user on any contraindications and any precautions to be taken. These details should in particular cover precautions to be taken in the event of breakage or changes in the performance of the pen-injector.

Annex A (informative)

Two-sided tolerance limit factors (k)

Table A.1 — 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
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