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
## Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foreword</td>
<td>iv</td>
</tr>
<tr>
<td>Introduction</td>
<td>v</td>
</tr>
<tr>
<td>1 Scope</td>
<td>1</td>
</tr>
<tr>
<td>2 Normative references</td>
<td>1</td>
</tr>
<tr>
<td>3 Terms and definitions</td>
<td>1</td>
</tr>
<tr>
<td>4 Symbols and abbreviations</td>
<td>3</td>
</tr>
<tr>
<td>5 General requirements</td>
<td>4</td>
</tr>
<tr>
<td>6 Test conditions</td>
<td>5</td>
</tr>
<tr>
<td>6.1 Standard atmosphere</td>
<td>5</td>
</tr>
<tr>
<td>6.2 Cool atmosphere</td>
<td>5</td>
</tr>
<tr>
<td>6.3 Hot atmosphere</td>
<td>5</td>
</tr>
<tr>
<td>7 Preconditioning of pen-injectors</td>
<td>6</td>
</tr>
<tr>
<td>7.1 Preconditioning in dry heat atmosphere</td>
<td>6</td>
</tr>
<tr>
<td>7.2 Preconditioning in cold storage atmosphere</td>
<td>6</td>
</tr>
<tr>
<td>7.3 Preconditioning in cyclical atmosphere</td>
<td>6</td>
</tr>
<tr>
<td>7.4 Preconditioning by free fall</td>
<td>6</td>
</tr>
<tr>
<td>7.5 Preconditioning by vibration for pen-injectors with electronic components</td>
<td>7</td>
</tr>
<tr>
<td>8 Reagent and apparatus</td>
<td>7</td>
</tr>
<tr>
<td>9 Determination of dose accuracy</td>
<td>7</td>
</tr>
<tr>
<td>9.1 Dose accuracy</td>
<td>7</td>
</tr>
<tr>
<td>9.2 Dose accuracy requirements</td>
<td>7</td>
</tr>
<tr>
<td>10 Freedom from defects</td>
<td>14</td>
</tr>
<tr>
<td>10.1 Defects after being subjected to cyclical preconditioning</td>
<td>14</td>
</tr>
<tr>
<td>10.2 Freedom from defects after being subjected to vibration</td>
<td>14</td>
</tr>
<tr>
<td>10.3 Freedom from defects after being subjected to free fall</td>
<td>14</td>
</tr>
<tr>
<td>11 Determination of electromagnetic compatibility</td>
<td>14</td>
</tr>
<tr>
<td>11.1 Electromagnetic compatibility (EMC)</td>
<td>14</td>
</tr>
<tr>
<td>11.2 Electrostatic discharge</td>
<td>15</td>
</tr>
<tr>
<td>11.3 Radiated radio frequency (RF) fields</td>
<td>15</td>
</tr>
<tr>
<td>12 Visual inspection</td>
<td>15</td>
</tr>
<tr>
<td>13 Functional inspection</td>
<td>16</td>
</tr>
<tr>
<td>13.1 Replaceable cartridge</td>
<td>16</td>
</tr>
<tr>
<td>13.2 Nonreplaceable cartridge</td>
<td>16</td>
</tr>
<tr>
<td>13.3 Accuracy</td>
<td>16</td>
</tr>
<tr>
<td>14 Test report</td>
<td>16</td>
</tr>
<tr>
<td>15 Information supplied by the manufacturer</td>
<td>16</td>
</tr>
<tr>
<td>15.1 General</td>
<td>16</td>
</tr>
<tr>
<td>15.2 Marking</td>
<td>17</td>
</tr>
<tr>
<td>15.3 Instructions for use</td>
<td>17</td>
</tr>
<tr>
<td>Annex A (informative) Two-sided tolerance limit factors (k)</td>
<td>19</td>
</tr>
<tr>
<td>Bibliography</td>
<td>25</td>
</tr>
</tbody>
</table>
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.


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**

\( V_{\text{set}} \) One of the three pre-set doses (expressed as a volume, in millilitres) used in determining the dose accuracy for a given pen-injector. \( V_{\text{set}} \) 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 \( V_{\text{mid}} \) 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.

\( V_{\text{meas}} \) The volumetric measurement value for a given \( V_{\text{set}} \)

\( G_{\text{meas}} \) The gravimetric measurement value for a given \( V_{\text{set}} \)
$\rho$ 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 $V_{\text{min}}$, $V_{\text{mid}}$, and $V_{\text{max}}$. There are six possible replicates.

$n$ Number of measurements ($V_{\text{meas}}$) to be made for each $V_{\text{set}}$

$\bar{x}$ The sample mean; when based on a random sample, an estimate of the true mean:

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

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

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

$k$ Tolerance Limit Factor, determined from the confidence level (95 %), probability content ($p$) and the number of accuracy measurements ($n$) conducted at each dose setting

$\alpha$ Absolute error (millilitres) used to define the upper and lower specification limits for a pre-set dose in absolute terms

$\beta$ 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 $V_{\text{set}}$ changes from absolute terms to relative terms:

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

$U$ Upper specification limit for a given $V_{\text{set}}$

$L$ Lower specification limit for a given $V_{\text{set}}$

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.