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2024-06

Prefilled syringes —

Part 4: Glass barrels for injectables and sterilized subassembled syringes ready for filling

Seringues préremplies —

Partie 4: Cylindres en verre pour produits injectables et seringues pré-assemblées stérilisées préremplissables

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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 document 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).

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This document was prepared by Technical Committee ISO/TC 76, *Transfusion, infusion and injection, and blood processing equipment for medical and pharmaceutical use*.

This fourth edition cancels and replaces the third edition (ISO 11040-4:2015), which has been technically revised.

The main changes are as follows:

— Clause 3 has been updated;

— update on general requirements have been added on quality systems, testing and documentation;

— additional requirements to specific components of sterilized subassembled syringes ready for filling have been revised;

— requirements on syringes barrels have been revised by:

  — addition of specification for finger flange breakage resistance,

  — addition of specification for cone breakage resistance,

  — addition of requirements specifically for staked needle syringes,

  — addition of performance requirements for non-lubricated syringes.

— figures in Annex A have been updated;

— information of former Annex B has been implemented in 5.1; new Annex B shows information of typical components of a finished prefilled syringe;

— general update of annexes.

A list of all parts in the ISO 11040 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

In the past, ampoules and injection vials were mainly used for (parenteral) injectable products. However, for the injection of the products contained in those ampoules and vials, a hypodermic syringe combined with the appropriate injection needle is also needed. This means the injectable product must be transferred by the user into the hypodermic syringe before its final use. This procedure is not only time-consuming, but also presents a great number of possibilities for contamination.

To ensure safe use of an injectable product, prefilled syringes for single use are on the market for many years. Without a doubt, such prefilled syringes permit immediate injection of the product contained after relatively simple handling. These syringes can also be used in injectors with automated functions where further and particular requirements apply.

Based on the diameter of the prefilled syringes, appropriate components, such as plunger stoppers, tip caps, needle shields, and other syringe closure systems can also be standardized. In conjunction with the right sealing components, they offer a system for (parenteral) injectable use. The producers of filling machines can use this document to standardize the equipment of the machines.

In the beginning of prefilled syringe processing by the pharmaceutical industry, syringes made of tubing glass were delivered to the pharmaceutical companies in the form of so called non-sterile “bulkware” only. The process steps washing, drying, inner surface lubrication, sealing the syringe with a syringe closure system, sterilization, as well as filling and closing, were then performed in the pharmaceutical companies. Processing of “bulkware” is still performed this way. Sterilized subassembled syringes have partially replaced non-sterile “bulkware”.

In the case of sterilized subassembled syringes ready for filling, responsibility for the aforementioned process steps relevant to the injectable product lies with the manufacturer of the primary packaging material. Following the assembly of the needle shield on syringes with a staked needle or tip caps for the Luer slip version, the subassembled syringes are placed into so called nests. The nests, in turn, are placed into a plastic tub. The syringes in the nest are protected against contamination by means of an insert liner and the tub itself is sealed by a sealing lid (which is currently and, so far, primarily achieved using a gas permeable material). Thus, the tub properly sealed with the sealing lid represents the “sterile barrier system”. The sealed tub is then wrapped into a sealable bag and, thus, ready for sterilization, which is currently and, so far, primarily performed using ethylene oxide.

In this form, the sterilized subassembled syringes ready for filling are delivered to the pharmaceutical companies in a sterile condition, where they are processed on suitable machines.

Prefilled syringes —

Part 4:
Glass barrels for injectables and sterilized subassembled syringes ready for filling

1 Scope

This document specifies materials, dimensions, quality, and performance requirements, as well as relevant test methods.

This document also specifies components that are part of the sterilized subassembled syringe ready for filling.

This document is applicable to

— tubing-glass barrels (single-chamber design) for injection preparations, and

— sterilized subassembled syringes ready for filling.

Glass barrels and sterilized subassembled syringes ready for filling in accordance with this document are intended for single use only.

Components to complete the subassembled syringe, such as plunger stopper and plunger rod, are outside the scope of this document.

NOTE National or regional regulations such as Ph.Eur., USP, or JP can apply.

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 720, *Glass — Hydrolytic resistance of glass grains at 121 °C — Method of test and classification*

ISO 4802-1, *Glassware — Hydrolytic resistance of the interior surfaces of glass containers — Part 1: Determination by titration method and classification*

ISO 4802-2, *Glassware — Hydrolytic resistance of the interior surfaces of glass containers — Part 2: Determination by flame spectrometry and classification*

ISO 7864:2016, *Sterile hypodermic needles for single use*

ISO 8871-1, *Elastomeric parts for parenterals and for devices for pharmaceutical use — Part 1: Extractables in aqueous autoclavates*

ISO 9626, *Stainless steel needle tubing for the manufacture of medical*

ISO 10993-1, *Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process*

ISO 10993-7, *Biological evaluation of medical devices — Part 7: Ethylene oxide sterilization residuals*

ISO 11040-5, *Prefilled syringes — Part 5: Plunger stoppers for injectables*

ISO 80369-1, *Small-bore connectors for liquids and gases in healthcare applications — Part 1: General requirements*

ISO 80369-7, *Small-bore connectors for liquids and gases in healthcare applications — Part 7: Connectors for intravascular or hypodermic applications*

ISO 80369-20, *Small-bore connectors for liquids and gases in healthcare applications — Part 20: Common test methods*

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 https://www.electropedia.org/

3.1
customer
business entity which purchases syringe barrels or sterilized subassembled syringes ready for filling and conducts further processing or filling as appropriate

3.2
Luer connector
small-bore connector that contains a conical mating surface with a 6 % (Luer) taper intended for use in intravascular or hypodermic applications of medical devices and related accessories

Note 1 to entry: A Luer connector can be either a Luer slip connector or a Luer lock connector.

Note 2 to entry: Male Luer connectors are referenced as cone and female Luer connectors are referenced as socket to align as recommended in ISO 80369-7.

EXAMPLE Hypodermic needle systems (ISO 7864).

[SOURCE: ISO 80369-7:2021, 3.2, modified — Note 2 to entry was deleted, a new Note 2 to entry and an example were added]

3.3
Luer lock adapter
Luer connector that contains a locking mechanism which is connected to a 6 % Luer slip

Note 1 to entry: See Figure 2.

3.4
manufacturer
business entity which performs or is otherwise responsible for the manufacturing of the syringe barrels (bulkware) or for the sterilized subassembled syringes ready for filling by the customer

3.5
needle shield
elastomeric syringe closure system, which seals the front end of staked needle syringe, designed to protect the needle tip/bevel from damage and allows sterilization of the syringe

3.5.1
rigid needle shield
needle shield (3.5) covered by a rigid housing

3.6
plunger stopper
elastomeric syringe closure, which seals the back end of the syringe

3.7
prefilled syringe
container system filled with the injectable product ready for injection

Note 1 to entry: Components of subassembled syringes ready for filling are illustrated in Annex A.

Note 2 to entry: Additional components for a subassembled syringe ready for filling are illustrated in Annex B.

3.8
sterilized subassembled syringe ready for filling
syringe that has been manufactured and sterilized

Note 1 to entry: The subassembly has been manufactured by applying the following processes, as applicable:

— glass barrel forming;

— (needle bonding for staked needle syringes);

— washing/drying;

— lubricant of inner surface of the syringe barrel (where applicable);

— (lubrication of needle for staked needle syringes);

— closure setting on front end;

— packing (see ISO 11040-7);

— sterilization.

Note 2 to entry: Examples of sterilized subassembled syringes ready for filling including components are illustrated in Annex A.

3.9
syringe barrel
cylindrical glass body with front end and finger flange as back end

Note 1 to entry: See Figure 1.

3.10
syringe closure system
elastomeric component or multi-component system designed to close the syringe system at the front end that is designed to allow sterilization of the subassembly

EXAMPLE *Tip cap* (3.11), *needle shield* (3.5), tamper-evident syringe closure system.

3.11
tip cap
elastomeric syringe closure system used with 6 % Luer slip front end

3.11.1
rigid tip cap
elastomeric *syringe closure system* (3.10) covered by a rigid housing which only works in combination with a 6 % Luer slip with a Luer lock mechanism for a Luer lock adapter

4 General requirements

4.1 Quality systems

The documentation and activities described within this document shall follow a formal quality management system.

NOTE ISO 15378 contains requirements for a suitable quality management system for primary packaging materials for medicinal products.

4.2 Testing

Test equipment shall be qualified and implemented test methods shall be validated. The sampling plans used for the selection and testing of sterilized subassembled syringes ready for filling or components thereof shall be based upon a statistically valid rationale.

Unless agreed otherwise, testing shall be performed at ambient laboratory conditions.

NOTE Examples of suitable sampling plans are given in ISO 2859-1 and the ISO 3951 series; see also Reference [14].

4.3 Documentation

Demonstration of conformity with the requirements of this document shall be documented.

All documentation shall be retained as defined in the used quality management system (e.g. ISO 15378:2017, 7.5.3[10]). The retention period shall consider factors such as regulatory requirements, expiration date and traceability.

Documentation of conformity with the requirements can include, but is not limited to, performance data, specifications, and test results from validated test methods.

Electronic records, electronic signatures, and handwritten signatures executed to electronic records that contribute to validation, process control, or other quality decision-making processes shall be documented (for example, as defined in ISO 15378:2017, 8.5[10]).

5 Syringe barrel

5.1 Design including dimensions

5.1.1 Dimensions for 6 % Luer slip and 6 % Luer slip for Luer lock adapter front end syringes

The dimensions of the syringe barrel shall be as shown in Figure 1 and as given in Table 1, except for the total barrel length and the wall thickness, which are given for information only.

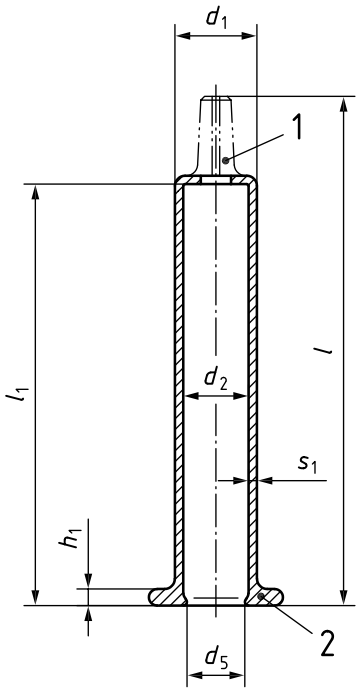
The type of front end shall be agreed upon between the manufacturer and the customer. For the 6 % Luer slip and the 6 % Luer slip for Luer lock adapter, ISO 80369-7 and ISO 80369-1 shall apply, and the dimension of the Luer conical fitting shall conform with Figure 2 or Figure 3.

NOTE Available syringe barrels are routinely made with Luer or Luer lock connection in order to enable connection to administration devices to effectively administer the drug product stored within the syringe. Examples are disposable needles, needleless connector devices, and other forms of Luer access. The current state of the art glass syringe front end forming technology cannot conform completely to the standards on Luer connectors (see ISO 80369-7).

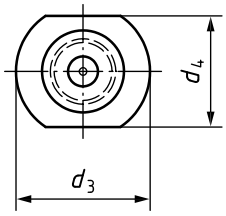
The dimensional tolerances in Figure 2 and Figure 3 (Luer slip diameter) differ from ISO 80369-7 because of the manufacturing methodologies and the need for expanded tolerances in the glass forming manufacturing process exist. While these tolerances are outside of the range of ISO 80369-7 with respect to some of the dimensions, the formed glass tip does successfully mate with injection moulded socket counterparts. See

5.2, ISO 80369-7 and ISO 80368-20 for functional test methods that accommodate for the formed Luer slip manufacturing process.

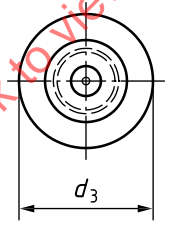
Luer slip dimensions mentioned in Figures 2 and 3, can be checked by means of camera measurements or indirectly by using a gauge similar to the one described in ISO 80369-7.



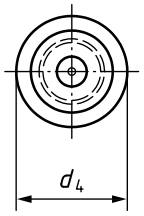
a) Syringe barrel



b) Cut flange



c) Large round flange



d) Small round flange

Key

1 front end

2 back end

The dimensions are given in Table 1.

NOTE 1 The bore diameter of the tip is subject to agreement between the manufacturer and the customer.

NOTE 2 The design of the finger flange is subject to agreement between the manufacturer and the customer.

Figure 1 — Example syringe barrel including types of finger flanges

Table 1 — Syringe barrel dimensions (see Figure 1)

Dimensions in millimetres

Nomi-nal volume ml	Glass barrel										Finger flange					
	d_1		d_2		d_5	l_1		l [c]		s_1 [c]	h_1		d_3		d_4	
	nom	tol	nom	tol	min.	nom.	tol.	nom.	tol.	≈	nom.	tol.	nom.	tol.	nom.	tol.
0,5	6,85		4,65	±0,1	4,40	47,6		57,5		1,1	1,8	±0,5	13,4	±0,4	10,5	±0,4
1[a]	8,15		6,35		6,05	54		64,0	±0,5	0,9	1,9		13,8		11	
1[b]	10,85	±0,1	8,65		8,25	35,7	±0,5	46,7		1,1	2,2		17,75		14,7	
1,5	10,85		8,65		8,25	43,2		55,4		1,1	2,2		17,75	±0,75	14,7	
2	10,85		8,65		8,25	49		60,0		1,1	2,2	±0,5	17,75		14,7	±0,5
2,25	10,85		8,65	0,2	8,25	54,4		66,6	±0,75	1,1	2,2		17,75		14,7	
3	10,85		8,65		8,25	72,2		84,4	±1,0	1,1	2,2		17,75		14,7	
5	14,45		11,85		11,45	66,7	±0,75	80,0	±0,75	1,3	2,4		23		19,5	
10	17,05	±0,2	14,25		13,85	87,25		100,5	±1,0	1,4	2,5	±0,6	27	±1	21,5	
20	22,05		19,05		18,40	96,8		114,9	±1,0	1,5	3,1		32,25		25,9	±0,6

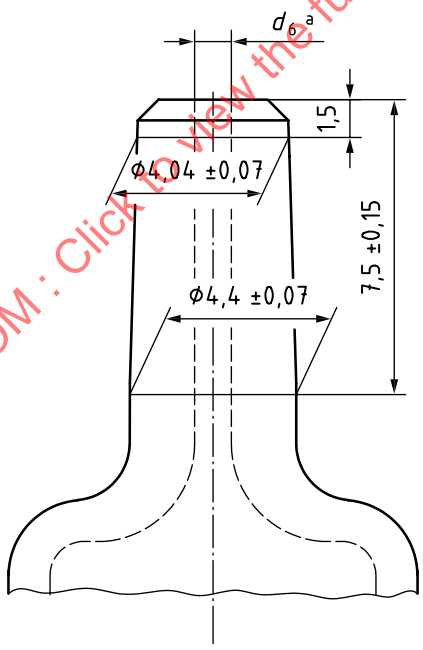
[a] Long version.

[b] Short version.

[c] Dimensions are for information only.

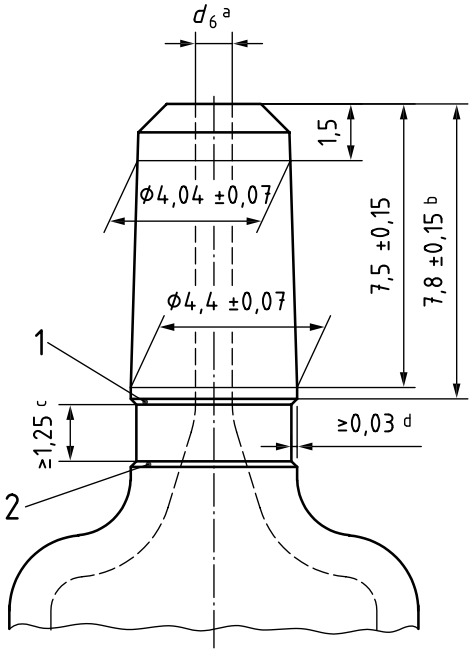
5.1.2 Specific dimensions for front end design for 6 % Luer slip and 6 % Luer slip for Luer lock adapter

Figure 2 and Figure 3 show detailed dimensions of the corresponding front end with 6 % Luer slip and 6 % Luer slip for Luer lock adapter.



[a] Through bore diameter shall be agreed between the manufacturer and customer.

Figure 2 — Front end design with 6 % Luer slip



Key

1 upper chamfer

2 lower chamfer

a Through bore diameter shall be agreed between the manufacturer and customer.

b Length of 6 % Luer slip for Luer lock adapter.

c Length of groove for Luer lock adapter.

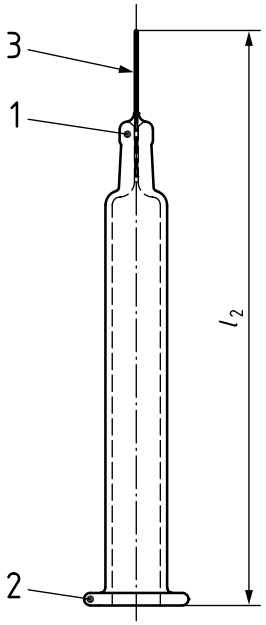
d Depth of groove for Luer lock adapter.

NOTE The lower chamfer is optional.

Figure 3 — Front end design with 6 % Luer slip for Luer lock adapter

5.1.3 Dimensions for staked needle (SN) syringes

The dimensions of the syringe barrel shall be as shown in Figure 4 and as given in Table 1, except the wall thickness, which is given for information only.



Key

1 front end

2 back end

3 staked needle

NOTE 1 The needle diameter and needle length are subject to agreement between the manufacturer and the customer.

NOTE 2 The design of the finger flange is subject to agreement between the manufacturer and the customer. Designs are shown in Figure 1.

Figure 4 — Example of a staked needle syringe

Table 2 — Staked needle syringe dimensions (see Figure 4)

Dimensions in millimetres

Nominal volume ml	SN barrel		
	Needle length mm (inch)	nom l_2 mm	max tol mm
0,5	12,7 (1/2")	70,2	±1,5
0,5	15, 8 (5/8")	73,4 to 73,5	
1[a]	8,0 (5/16")	72	
1[a]	12,7 (1/2")	76,7	
1[a]	15, 8 (5/8")	79,9 to 81,0	
1[a]	25,4 (1")	89,4	
1[b]	12,7 (1/2")	59,4	
1[b]	15, 8 (5/8")	62,6 to 63,5	
1[b]	25,4 (1")	72,1	
1,5	12,7 (1/2")	66,7 to 66,9	
1,5	15, 8 (5/8")	69,9 to 70,8	
1,5	25,4 (1")	79,4	
2,25	8,0 (5/16")	73,5	
2,25	12,7 (1/2")	78,1 to 78,3	
2,25	15, 8 (5/8")	81,4	

[a] Long version.

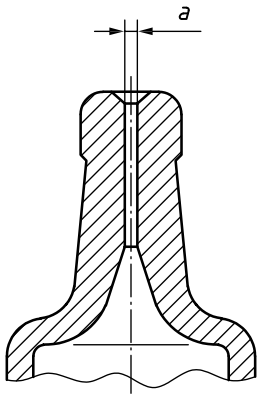
[b] Short version

NOTE 1 Barrel dimensions for SN syringes are the same as listed in Table 1.

NOTE 2 1 inch = 25,4 mm.

5.1.4 Front end design for staked needle syringe

Figure 5 shows a typical front end design for a staked needle syringe.



[a] Diameter depending on needle size.

Figure 5 — Example of a front end design for a staked needle syringe

5.2 Functional testing of Luer connection

The functional performance of the glass syringe barrel with regard to the conical connection to a 6 % Luer socket connector fitting shall be demonstrated through performance testing with the socket reference connectors made of plastic instead of steel.

NOTE The forming process of glass syringe front end can result in a “wavy” Luer connector surface finish that is incompatible with the use of steel reference connectors for liquid and air leakage, separation force, and unscrewing torque type tests. In addition, the 6 % Luer slip of glass syringe barrels are often roughened on customer request.

For the purpose of demonstrating the functional performance of the syringe Luer connection and the equivalent safety of the connection, a plastic reference connector shall conform with the dimensional requirements of ISO 80369-7.

The selected plastic material for the reference connectors shall be chosen for being representative for the normal use condition for injection. A rationale shall be developed for the selection of material(s).

5.3 Material

The material of the syringe barrel shall be colourless (cl) or amber (br) glass of the hydrolytic resistance grain class HGA 1 in accordance with ISO 720.

Material requirements are also covered by national or regional pharmacopoeias. See, for example, requirements for glass Type I in Ph.Eur. 3.2.1[17], USP <660>[24] and in JP 7.01[37].

5.4 Performance requirements

5.4.1 Hydrolytic resistance glass barrel

Hydrolytic resistance of syringe barrel shall be determined in accordance with ISO 4802-1 or ISO 4802-2.

Syringe barrel requirements are also covered by national or regional pharmacopoeias. See, for example, requirements for glass Type I in Ph.Eur. 3.2.1[17], USP <660>[24] and in JP 7.01[37].

5.4.2 Annealing quality

The maximum residual stress shall not produce an optical retardation exceeding 40 nm/mm of glass thickness when the syringe barrel is viewed in a strain viewer.

The test method for residual stress is subject to agreement between the manufacturer and the customer.

5.4.3 Lubrication of the inner surface

For syringe barrels whose inner surfaces have been lubricated, 6.5.1.2 shall apply.

5.4.4 Flange breakage resistance

Syringe barrels shall provide an appropriate flange breakage resistance. Depending on the intended use the finger flange breakage resistance requirements shall be discussed between manufacturer and customer.

The flange breakage resistance shall be determined in accordance with C.1.

The flange breakage resistance for all finger flange designs, as shown in Figure 1, shall be ≥35 N.

NOTE The design of the finger flange can result in different breakage resistance forces. The breakage resistance forces from lowest to high are: cut flange lower than large round flange lower than small round flange [Figure 1 b) < Figure 1 c) < Figure 1 d)].

5.4.5 Front end breakage resistance

Syringe barrels shall provide an appropriate front end breakage resistance.

The front end breakage resistance for Luer slip syringe barrels (see Figure 2 and Figure 3) after the forming process prior to additional processing shall be ≥30 N.

The front end breakage resistance shall be determined in accordance with C.2.

NOTE The method described in C.2 can also be used to determine front end breakage resistance of staked needle syringes prior to additional processing (Figure 5).

6 Sterilized subassembled syringes ready for filling

6.1 General

6.1.1 Design

The design and testing of sterilized subassembled syringes ready for filling varies due to their intended use.

If printing on the syringe barrel is required, it shall be agreed between the manufacturer and the customer.

NOTE Common types of sterilized subassembled syringes ready for filling are illustrated in Annex A.

6.1.2 Raw materials properties

The following properties should be considered when selecting the raw materials or components and the design for the sterilized subassembled syringe ready for filling:

a) biocompatibility and toxicological attributes;

b) physical and chemical properties;

c) ability for sterilization and compatibility with respect to the intended sterilization process;

d) maintenance of sterility of the subassembly;

e) functionality for their intended use;

f) robustness of the syringe closure system during transport from the manufacturer to the customer.

6.1.3 Documentation

The manufacturer shall have documented procedures for the design and development of sterilized subassembled syringes ready for filling.

NOTE ISO 15378 contains requirements for a quality management system for primary packaging materials for medicinal products.

6.2 Sterility

Sterilized subassembled syringes ready for filling shall have been sterilized to a sterility assurance level (SAL) of 10^{-6} using a suitable validated sterilization method (see ISO 11135, ISO 17665-1, the ISO 11137 series or ISO 14937).

The sterilization process shall not compromise the safety and performance (i.e. changing of colours, dimensions, forms, closing or sealing, blooming or detachment of components, etc.) of the subassembled syringe.

NOTE Sterility testing is subject of national or regional pharmacopoeias. See the methods given in Ph.Eur., 2.6.1[18], USP <71>[25] and JP 4.06[35].

For ethylene oxide sterilization, the requirements for residuals given in ISO 10993-7 shall apply. See also Reference [16].

6.3 Pyrogenicity/endotoxins

For pyrogenicity, the limit value for syringes shall be <0,25 EU/ml, considering the nominal volume according to Table 1 or Table 2.

NOTE 1 For rationale, see USP monograph on sterile water for injection according to USP <1231>[27].

NOTE 2 Extraction method and testing are specified in regional and national pharmacopoeias:

— for extraction method, see USP <161>[27];

— for testing, see Ph.Eur., 2.6.14, method c)[22], USP <85>[28] and JP 4.01[33].

NOTE 3 A sample preparation procedure is given in D.1. This is based on applicable pharmacopoeias.

The subassembled syringes ready for filling shall be processed to remove pyrogenic properties to ensure that they are suitable for their intended use. Such processes shall be validated for three log endotoxin reduction.

6.4 Particulate matter

Sterilized subassembled syringes ready for filling shall be manufactured by processes that reduce the risk of particulate contamination of the intended content.

Current pharmacopoeias identify visible particulates for parenteral preparations and water for injection as undesirable but do not define the size or put a limit on the allowable number. The manufacturer and the customer should agree upon the size and number of visible particles and the test method.

The particle-related specifications given in pharmacopoeias (e.g. Ph.Eur., USP, JP) do not apply to empty containers. In order but to show a certain cleanliness level, the following limits for sub-visible particles shall apply:

— particles ≥10 µm: 600 max. per syringe;

— particles ≥25 µm: 60 max. per syringe.

NOTE 1 These limits have been derived from the USP <788>[30] (small volume parenterals) limit values for filled containers with a nominal volume of less than 100 ml. The limit of the subassembly, which is 10 % of the USP <788>[29], have been chosen based on historical proven capability using the light obscuration method as given in D.2.

If syringes would be used for ophthalmic solutions, the particulate matter specification should be discussed between manufacturer and customer.

NOTE 2 See also Ph.Eur. 2.9.19[19], Ph.Eur. 2.9.20[20], USP <788>,[29] JP 6.06,[35] and JP 6.07[36].

6.5 Additional requirements to specific components of sterilized subassembled syringes ready for filling

6.5.1 Syringe barrel

6.5.1.1 General

The requirements given in Clause 5 shall apply.

Specific design features of the syringe barrel should be agreed between the manufacturer and the customer.

6.5.1.2 Lubricated syringes

The inner surface of the syringe barrel may be lubricated. Limit values of the amount of lubricant are subject to agreement between the manufacturer and the customer.

NOTE 1 Lubrication of the inner surface of the syringe barrel is applied in order to improve gliding properties. This is usually done by siliconization (i.e. by application of a silicone oil to the inner glass surface or with silicone emulsion followed by heat treatment).

If silicone oil is used, applicable requirements in pharmacopoeias can apply (see, for example, References [23] and [32]).

NOTE 2 Annex E includes a suitable test method for the determination of the quality and consistency of the syringe lubrication using a gliding force test.

NOTE 3 The following are examples of test methods for visualizing the quality of the inner surface treatment:

— the homogeneity of the siliconization can be checked by using aluminium oxide powder or alternative powder of a defined quality; in this test, a defined powder is distributed within the syringe barrel by shaking. Spots with powder indicate insufficient siliconization;

— optical test methods.

6.5.1.3 Lubrication-free syringes

Lubrication-free syringes do not have any gliding properties on their own. Gliding properties will only be achieved in combination with a special plunger stopper/piston where these plunger stoppers act as lubrication.

NOTE Annex E includes a suitable test method for the determination of the quality and consistency of the plunger stopper lubrication performance using a gliding force test.

6.5.1.4 Dead space

A method for the determination of dead space with the plunger stopper/piston fully inserted is given in ISO 7886-1:2017, Annex C.

6.5.2 Needle

6.5.2.1 General

If the sterilized subassembled syringe ready for filling is delivered with a staked needle front end, the requirements in 6.5.2.2 to 6.5.2.6 shall apply for the needle.

6.5.2.2 Material and dimension

The needle tubing shall fulfil material and dimensional, requirements in accordance with ISO 9626. Specific design features of the needle, e.g. bevel type, should be agreed upon between the manufacturer and the customer.

6.5.2.3 Surface treatment

The needle can be surface-treated using a lubricant (e.g. silicone oil) to minimize pain when the needle penetrates, for example, the skin during the injection.

For silicone oil, requirements in pharmacopoeias can apply (see, for example, References [23] and [32]).

6.5.2.4 Penetration force

The limit for needle penetration force into a test foil should be <3 N for needle diameters ≤ 0,70 mm (G22).

NOTE 1 A suitable test method for the determination of the needle penetration force is given in Annex F.

NOTE 2 Needle penetration force measurements can be useful to detect needle point and lubrication defects but might not be correlated with injection pain.

6.5.2.5 Needle lumen patency

The manufacturer shall ensure that the inner needle diameter of the finished prefillable staked needle syringe meets the specifications in ISO 9626 after all processing. This shall be done as part of the validation of the design and process. This can be done through determination that a stainless-steel stylet of the appropriate diameter selected from the diameters given in ISO 7864:2016, Table 3 passes through the needle. Another method is a comparison of the flow rate of air or water through the needle against an unprocessed needle tube of equivalent outer diameter and length having a minimum inner diameter in accordance with ISO 9626 when tested under the same pressure.

6.5.2.6 Needle bonding and bonding strength

The adhesive used for fixing the needle inside the front end design of staked needle syringes shall fulfil the requirements of ISO 10993-1.

The fixation of the needle in the glass cone shall be tested in accordance with G.1.

Bonding strength between glass and the needle shall be:

a) ≥40 N for 0,70 mm (G22) needles,

b) ≥34 N for 0,60 mm (G23) needles,

c) ≥34 N for 0,55 mm (G24) needles,

d) ≥22 N for 0,50 mm (G25) needles,

e) ≥22 N for 0,45 mm (G26) needles,

f) ≥22 N for 0,40 mm (G27) needles,

g) ≥22 N for 0,36 mm (G28) needles,

h) ≥22 N for 0,33 mm (G29) needles, and

i) ≥11 N for <0,33 mm (G30 and above) needles.

NOTE 1 Bonding strength values are given in ISO 7864.

NOTE 2 Depending on the intended use, the bonding strength can be discussed between the manufacturer and the customer.

6.5.3 Syringe closure system

6.5.3.1 Design

The design of the front end syringe closure system shall be such that

— tip caps (if used) can be removed from the syringe with a reasonable torque,

— tip caps or needle shields (as applicable) can be removed from the syringe with a reasonable pull-off force, and

— tip caps or needle shields maintain the sterility of the front end.

6.5.3.2 Materials

The rubber material in contact with the injectable product shall be in accordance with the applicable requirements of ISO 8871-1.

NOTE For additional regional or national requirements of pharmacopoeias, see type I or type II requirements of Ph.Eur. 3.2.9[21], USP <381>[30].

6.5.3.3 Sterilization

The syringe closure system shall allow for sterilization. Conformity shall be demonstrated by suitable methods.

6.5.3.4 Liquid leakage

The syringe closure system shall provide an appropriate liquid leakage resistance when tested in accordance with G.2.

Limit values are subject to agreement between the manufacturer and the customer.

6.5.3.5 Luer connectors/Luer lock adapters

Socket Luer connectors, e.g. the conical socket of the hypodermic needle hub shall conform with dimensional and functional requirements as specified in ISO 80369-7 and ISO 80369-20.

Luer lock adapter (LLA) used with syringes as shown in Figure 2 shall conform with following functional requirements:

— withstand a pull-off force of at least 22 N, when tested in accordance with G.3;

— withstand a minimum torque resistance of at least 3 Ncm, when tested in accordance with G.4.

6.5.3.6 Unscrewing and pull-off forces

The maximum allowed torque and the pull-off force shall be agreed upon between the manufacturer and the customer.

The test(s) shall be performed in accordance with G.5 and G.6, respectively.

6.6 Syringe closure system tightness

The components of sterilized subassembled syringes ready for filling shall provide sealing against each other during storage and transport.

The tightness test in Annex H is a valuable method to test the tightness of a sterilized subassembled syringe ready for filling in the design development phase.

NOTE Helium leak testing can be used for the component evaluation of front end syringe closure systems as well as for back end plunger stoppers. Information on Helium leak testing as well as other suitable methods is given in USP <1207>[31].

7 Packaging

Non-sterile glass barrels shall be packed in plastic trays as agreed upon between the manufacturer and the customer.

For packaging systems for sterilized subassembled syringes ready for filling, see ISO 11040-7.

8 Labelling

For labelling of packaging for sterilized subassembled syringes ready for filling, see ISO 11040-7.

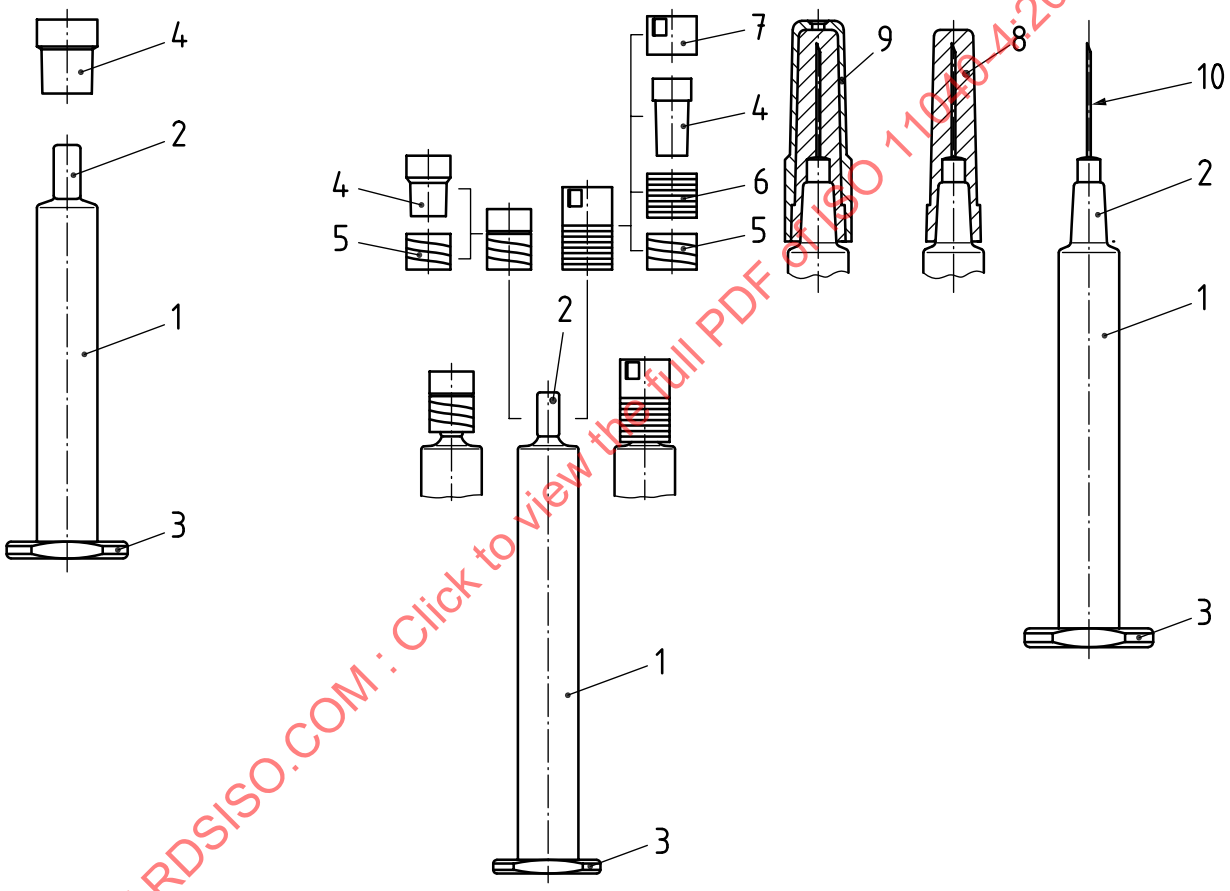
Labelling of packaging of non-sterile glass syringe barrels (bulkware) is subject to agreement between the manufacturer and the customer.

Annex A
(informative)

Examples of types of sterilized subassembled syringes ready for filling

A.1 Components

Figure A.1 a), Figure A.1 b), and Figure A.1 c) illustrate common components of sterilized subassembled syringes ready for filling.



a) 6 % Luer slip syringe **b) 6 % Luer slip syringe for Luer lock adapter** **c) Staked needle syringe**

Key

1	syringe barrel	6	rigid sleeve for (5)
2	front end	7	rigid cap
3	back end	8	needle shield (soft)
4	tip cap	9	rigid cap for (8)
5	Luer lock adapter	10	staked needle

Figure A.1 — Examples of sterilized subassembled syringes ready for filling including components of syringe closure systems

A.2 Description of front end syringe closure systems

A.2.1 General

Closure components close the syringe such that the injectable product remains entirely enclosed and that microbiological contamination of the content of the syringe is avoided. The closure components are mounted onto the syringe body of the sterilized subassembled syringe ready for filling by the manufacturer. This subassembly is then packed in a suitable packaging system and then sterilized by ethylene oxide or another method.

Examples of front end syringe closure systems are given in Figure A.1 a), Figure A.1 b), and Figure A.1 c).

A.2.2 Closures for syringes with 6 % Luer slip

Syringes with Luer cones are closed with a tip cap of an appropriate elastomeric material.

The seating of the tip cap is ensured by static friction between the socket cone of the tip cap and the cone of the glass syringe and can be improved by ceramic coating or roughening of the cone surface.

For schematic illustration, see Figure A.1 a).

A.2.3 Closures for syringes with 6 % Luer slip for Luer connectors

Syringes with Luer lock cone are closed with a tip cap of an appropriate elastomeric material. These tip caps can be embedded in rigid housings which are connected to the Luer lock adapters. The Luer lock adapter is snapped onto the 6 % Luer slip.

These rigid syringe closure systems are available with or without tamper evidence in various designs.

For schematic illustration, see Figure A.1, b).

A.2.4 Closures for syringes with staked needle

Syringes with a staked needle are closed with a needle shield or a rigid needle shield.

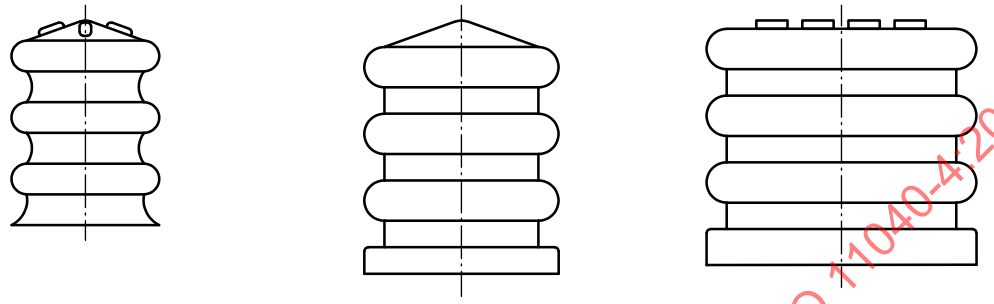
The needle tip, and particularly the opening of this tip, shall completely be embedded into the elastomer of the needle shield to ensure sealing.

For schematic illustration, see Figure A.1 c).

Annex B
(informative)

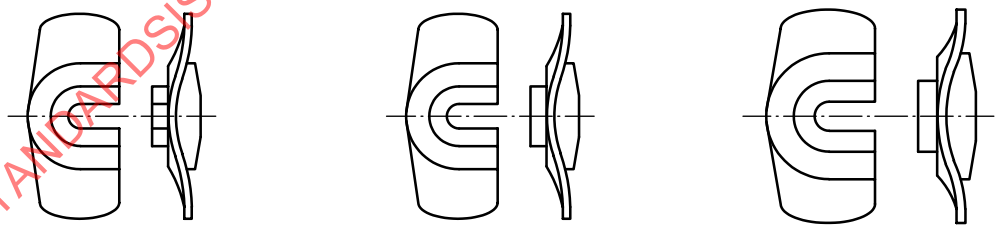
Additional components for a subassembled syringe ready for filling

See Figure B.1 for an example of additional components needed for testing.



a) Plunger stopper/piston variants

b) Plunger rod/piston rod example



c) Finger flange extensions/backstops

Figure B.1 — Typical components with prefilled syringes

Annex C
(normative)

Test methods for syringe barrels

C.1 Flange breakage resistance

C.1.1 Principle

The test is used to determine the flange breakage resistance by applying a force on a syringe barrel that has been placed in a cylinder holder under the flange.

Whenever a test method requires a peak measurement, a higher sampling rate (in Hz) will result in a more accurate result. Therefore, a sampling rate of 500 Hz is recommended for such tests. For all other tests, a sampling rate of minimum 100 Hz is recommended.

C.1.2 Materials

C.1.2.1 Syringe barrels to be tested, numbers as required.

NOTE Test is valid for syringe barrel as well as for sterile subassembled syringes ready for filling.

C.1.3 Apparatus

C.1.3.1 Universal tensile and compression testing machine conforming with the following:

— load cell appropriate to the force to be measured;

— test speed of 100 mm/min or as appropriate.

Attention shall be paid on bench overall rigidity for high-level resistance.

NOTE The definitions of load cell and test speed are subject to agreement between the manufacturer and the customer.

C.1.3.2 Syringe holder, made of an appropriate material [e.g. polyether ether ketone (PEEK)] and of appropriate dimensions.

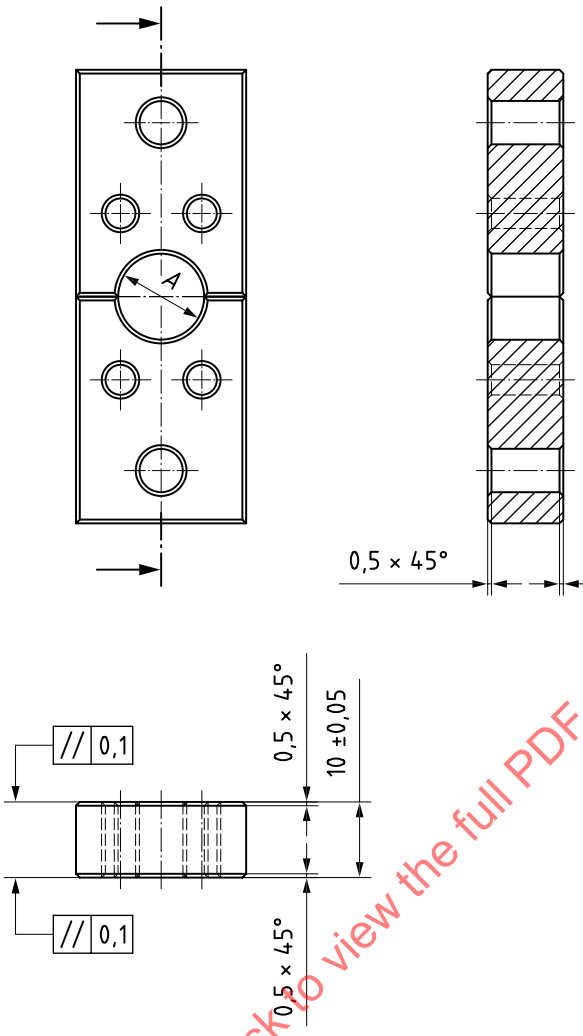
NOTE Materials and design depend upon the intended use. This is subject to agreement between the manufacturer and the customer. Table C.1 and Figure C.1 include examples for dimensions of a syringe holder.

Table C.1 — Examples for dimensions of the syringe holder and loading pin

Dimensions in millimetres

Syringe barrel outer diameter	Diameter *A* (see Figure C.1)	Diameter *b* (see Figure C.2)	Radius *c* (see Figure C.2)
6,85	7,3	4	2
8,15	8,6	5	2,5
10,85	11,4	7	6
14,45	15,0	10	8
17,05	17,5	12	9
22,05	22,5	16	11

Dimensions in millimetres



NOTE For diameter *A*, see Table C.1

Figure C.1 — Example of a syringe holder

C.1.3.3 Loading pin, made out of an appropriate material and of appropriate dimensions.

NOTE 1 Materials and design (e.g. radius of curvature adjusted to the internal syringe shoulder design) depend upon the intended use. This is subject to the agreement between the manufacturer and the customer. Table C.1 and Figure C.2 include examples for dimensions of the loading pin.

NOTE 2 Polyacetale, shore hardness D according to ISO 7619-1 between 80 and 90 is a suitable material of the contact area of the loading pin. The rod can be made of stainless steel.

C.1.4 Preparation and preservation of test samples

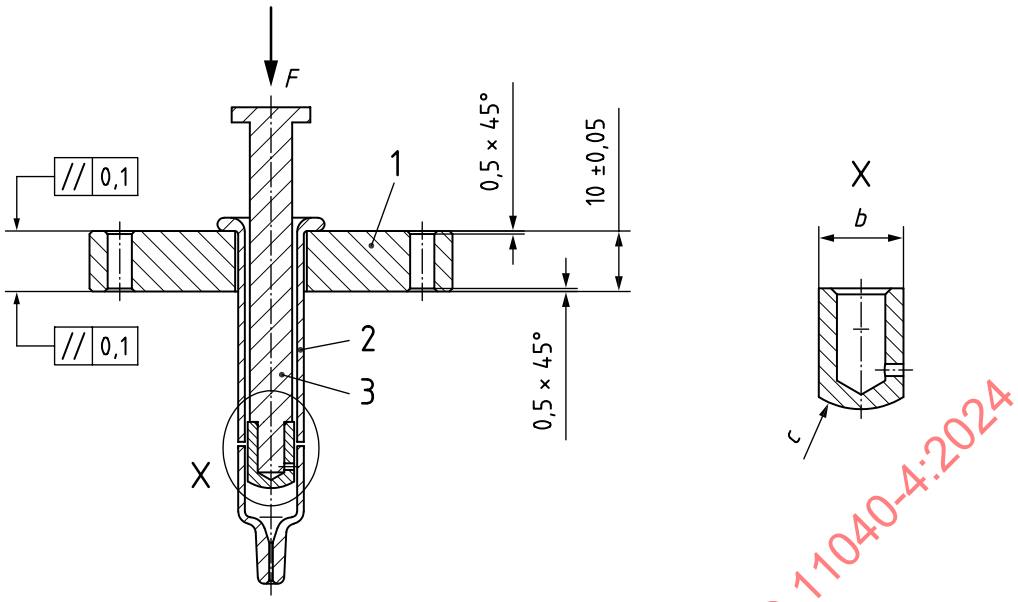
Do not shock the test samples before testing.

Inspect the syringe holder and the loading pin for damage prior to testing and change regularly.

C.1.5 Procedure

C.1.5.1 Place the syringe barrel to be tested in the syringe holder and position the loading pin close to the syringe barrel depth as illustrated in Figure C.2.

Dimensions in millimetres



Key

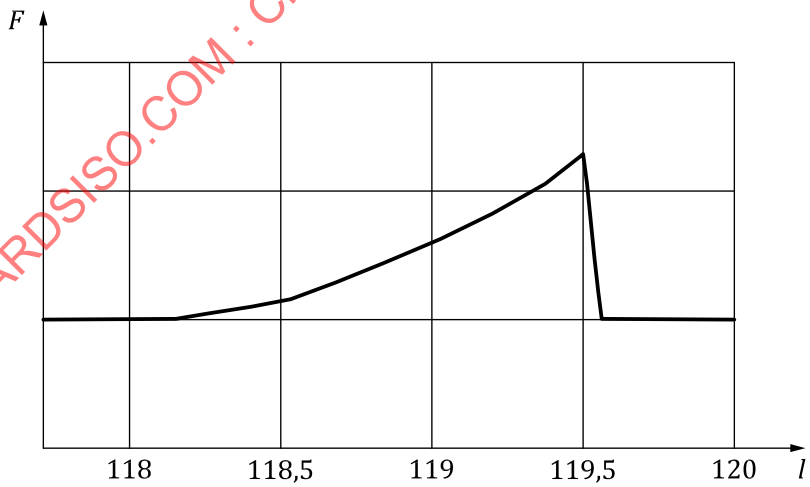
1 syringe holder
2 syringe barrel
3 loading pin

For diameter *b* and radius *c*, see Table C.1.

Figure C.2 — Placement of the syringe barrel and the loading pin

C.1.5.2 Start the test by applying a test speed of 100 mm/min or as appropriate.

C.1.5.3 Record the force versus displacement and prepare a graph. An example is given in Figure C.3.



Key

F force, in newtons
l distance, in millimetres

Figure C.3 — Example of a force versus displacement curve

C.1.6 Expression of results

Determine the peak value from the displacement curve. This corresponds to the flange breakage resistance (flange strength).

C.1.7 Test report or documentation

The test report or documentation shall include or refer the following:

— the test speed (mm/min);

— the peak value from the force versus displacement curve for each sample (N);

— the numbers of samples tested;

— any deviations or observations.

NOTE If the software does not allow to print all setup parameters, the traceability of all required parameters is given by additional documentation.

C.2 Front end breakage resistance

C.2.1 Principle

During standard usage and handling of syringes one weak point can be the front end of the syringe that can be charged by a side load and lead to breakage.

The front end breakage resistance test is used to determine the strength of the front end for designs described in Figure 2, Figure 3 and Figure 5 that is determined by the geometry and glass characteristics such as residual tension.

Whenever a test method requires a peak measurement, a higher sampling rate (in Hz) will result in a more accurate result. Therefore, a sampling rate of 500 Hz is recommended for such tests. For all other tests, a sampling rate of minimum 100 Hz is recommended.

C.2.2 Materials

C.2.2.1 **Syringe barrels to be tested,** numbers as required.

NOTE Test is valid for syringe barrel as well as for sterile subassembled syringes ready for filling

C.2.3 Apparatus

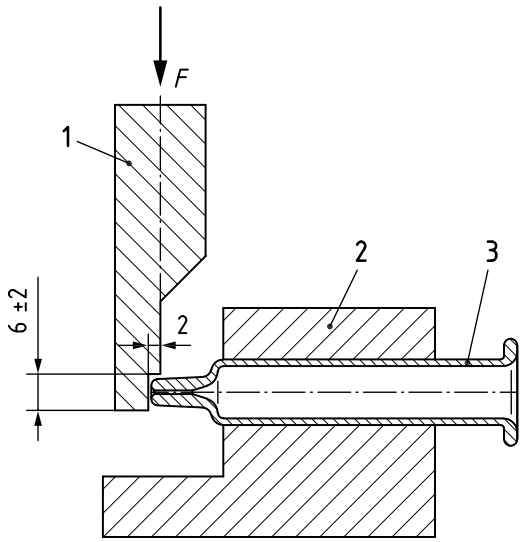
C.2.3.1 **Universal tensile and compression testing machine** conforming with the following:

— load cell appropriate to the force to be measured;

— test speed of 25 mm/min or as appropriate.

C.2.3.2 **Material holder and rod made of stainless steel**, with dimensions in accordance with Figure C.4.

Dimensions in millimetres



Key

1 compression testing machine with loading pin
2 syringe holder
3 syringe barrel
F force, in newtons

Figure C.4 — Example of a tensile and compression testing machine including holder with the syringe barrel inserted

C.2.3.3 Set of adapter parts that fit into the syringe format geometry

C.2.4 Procedure

C.2.4.1 Setup the test apparatus as follows:

— check the adapters for damage and correctness;

— assemble the adapters to the tensile and compression testing machine;

— check for security elements, glass breakage will occur;

— install and open correct software to the tensile and compression testing machine, if required.

C.2.4.2 Perform the test as follows:

— place the syringe barrel in the tensile and compression testing machine (see Figure C.4);

— close the security elements;

— start the measurement applying a test speed of 25 mm/min, or as appropriate,

— charge the syringe barrel until the front end breaks; apply the force at a distance of approximately 2 mm from the tip of the syringe barrel front end;

— remove the syringe barrel from the adapter;

— clean the adapter from glass residuals;

— make sure that it breaks at the front end.

C.2.5 Expression of results

Record the maximum force at which the front end breaks.

C.2.6 Test report or documentation

The test report or documentation shall include the following:

— test speed (mm/min);

— distance from the tip of the point where the syringe is charged (mm) (approximately 2 mm);

— maximum force at breakage (N);

— number of samples tested;

— any deviations or observations.

NOTE If software does not allow to print all setup parameters, that traceability of all required parameters is given by additional documentation.

Annex D
(informative)

Sample preparation for endotoxin and particulate determination

D.1 Endotoxins

D.1.1 General

The sample preparation for endotoxin determination is based on the following documents:

— guidance for industry, pyrogen and endotoxins testing, questions and answers[38];

— USP <161>[27];

— USP <85>[28];

— AAMI ST72:2019[12].

D.1.2 Materials and equipment

D.1.2.1 Sterilized syringes (i.e. sterilized by ethylene oxide or moist heat), not less than 3 and not more than 10 syringes.

D.1.2.2 Plunger stopper, endotoxin-free or has a vendor-certified maximum endotoxin level.

D.1.2.3 Endotoxin-free water of injection or *Limulus Amebocyte Lysate (LAL)* reagents, as extraction fluid having a temperature of (37 ± 1) °C or at room temperature.

D.1.2.4 Shaker.

D.1.2.5 Endotoxin-free container.

D.1.3 Procedure

D.1.3.1 Protect the endotoxin-free container from environmental contamination until analysed, i.e. work in a controlled environment such as ISO class 5 according to ISO 14644-1.

D.1.3.2 Fill the syringes with extraction fluid up to the nominal fill volume of the syringe.

D.1.3.3 Close the syringes with the plunger stopper.

D.1.3.4 Store the filled and closed syringes for not less than 1 h at room temperature.

D.1.3.5 Shake the syringes vigorously for 10 min on a horizontal shaker (or similar device).

D.1.3.6 Pool the extract into an endotoxin-free container by pushing the plunger stopper and empty the syringes through the front end (Luer cone, staked needle).

D.1.3.7 Determine the number of endotoxin units (EU/ml) of the extract including “positive” and “negative” samples.

NOTE See for example the method given in USP <85>[28].

The limit of the extraction fluid can be calculated according to USP <161>[27] using Formula (D.1):

$$\frac{KxN}{V} \tag{D.1}$$

where

K is the amount of endotoxin allowed per syringe;

N is the number of devices tested;

V is the total volume of extract rinse.

Ensure that the sensitivity of test reagent is high enough to allow a proper detection limit of endotoxins for pooled samples.

For 1 ml nominal fill volume and an endotoxin limit <0,25 EU/ml and a sensitivity of the reagent of 0,02 EU/ml, the "alarm" limit for 10 pooled syringes would be 0,20 EU/ml which is <0,25 EU/ml.

D.2 Particulates

D.2.1 General

The sample preparation of particulate matter determination is based on USP <788>[29] and Ph.Eur. 2.9.19[19].

D.2.2 Materials and equipment

D.2.2.1 Sterilized syringes (i.e. sterilized by ethylene oxide or moist heat), numbers as required.

D.2.2.2 Plunger stopper and plunger rod, numbers as required.

D.2.2.3 Water, for injection or any grade of purified water.

D.2.2.4 Container.

D.2.3 Procedure

D.2.3.1 Protect the container from environmental contamination until analysed, i.e. work in a controlled environment, e.g. ISO class 5 according to ISO 14644-1.

D.2.3.2 Prepare particle-free water by filtration of water for injection or any grade of purified water through a 0,2 µm to 0,8 µm pore-size filter unit.

D.2.3.3 Rinse all the needed equipment (e.g. beakers, dosage systems) with particle-free water.

D.2.3.4 Transfer a minimum of 30 ml of particle-free water into a cleaned container and let it rest undisturbed for a minimum of 2 min to allow degassing of air bubbles.

D.2.3.5 Determine the particle content of the particle-free water but disregard the first measurement as it is only used to clean the measurement system.

D.2.3.6 The limits for the particle-free water by light obscuration are

— 10 particles ≥10 µm, and

— 2 particles ≥25 µm.

If the particle content is within the limit, continue with the sample preparation.

If the particle content is not within the limit, repeat the filtration and measurement until the particle-free water is within specification (D.2.3.2 to D.2.3.5).

D.2.3.7 Fill the syringes with nominal volume and close with clean plunger stopper.

D.2.3.8 Invert the syringes 20 times.

NOTE It can be necessary to agitate the solution more vigorously to suspend the particles properly.

D.2.3.9 Remove the syringe closure system and dispense the contents of the syringes into a cleaned container by depressing the plunger with a plunger rod.

D.2.3.10 Let the solution rest undisturbed for a minimum of 2 min to allow degassing of air bubbles.

D.2.3.11 Determine the particle content per syringe but disregard the first measurement as it is only used to clean the measurement system.

The limits for the containers by light obscuration are given in 6.4.

NOTE A minimum pooled sample volume of 25 ml is needed to perform four runs of 5 ml each with 5 ml spare. The first run is always discarded. The average is calculated for the remaining three test runs. Depending on the nominal fill volume of the syringes, a certain amount of syringes is needed for a 25 ml pool.

To avoid air bubbles in the measuring device, it is recommended to add an extra 5 ml to the pool (30 ml pool volume).

Depending on the batch size of the syringes produced, multiple pools can be required.

The number of particles in each container can be calculated using Formula (D.2):

$$\frac{P \times V_t}{V_a \times n} \tag{D.2}$$

where

P is the average particle count obtained from the portion of container;

V_t is the volume of pooled sample (ml);

V_a is the nominal volume of each portion analysed (ml);

N is the number of containers pooled.

Annex E
(informative)

Glide force test method

E.1 Purpose

This test method is used to measure either the gliding force of empty syringe barrels to assess the quality and consistency of the, for example, silicone oil lubrication within the inner syringe barrel or to measure the glide force of non-lubricated syringes in combination with plunger stoppers acting as lubrification. The quality and consistency of the lubrication performance can be dependent on the test speed used.

NOTE 1 Typically, a test speed of 100 mm/min (similar to ISO 7886-1) is used; however, it can be insufficient to detect lubrication defects. The test speed is subject to agreement between the manufacturer and the customer.

NOTE 2 Non-lubricated syringes can also be tested as, e.g., water for injection (WFI) filled syringes to simulate intended use since dry testing might show different gliding performance than lubricated ones.

Whenever a test method requires a peak measurement a higher sampling rate (in Hz) will result in a more accurate result. Therefore, a sampling rate of 500 Hz is recommended for such tests. For all other tests, a sampling rate of minimum 100 Hz is recommended.

E.2 Materials

E.2.1 Empty sterilized subassembled syringes ready for filling, numbers as required.

NOTE Test is valid for syringe barrel as well as for sterile subassembled syringes ready for filling.

E.2.2 Plunger stopper in ready-to-use format, to be agreed upon between the manufacturer and the customer (dimensions, compound, siliconization level, sterilization).

E.2.3 Plunger rods, appropriate for use with selected plunger stopper, to be agreed upon between the manufacturer and the customer.

E.3 Apparatus

E.3.1 Universal tensile and compression testing machine conforming with the following:

— test speed of 100 mm/min or as appropriate;

— force range up to 50 N or as appropriate.

NOTE The definitions of test speed and force range are subject to agreement between the manufacturer and the customer.

E.3.2 Syringe support and syringe adaptor plates, appropriately sized for the sterilized subassembled syringes ready for filling to be tested.

E.3.3 Vent tube stoppering or vacuum stoppering tool or machine.

E.4 Procedure

E.4.1 Set the plunger stopper in the empty syringe barrel by using the vent tube insertion or vacuum stoppering method. Select stopper position(s) based on the following areas of concern:

— focus on front portion of barrel; sensitive area for auto-injector performance: Select a position corresponding to 50 % of nominal fill volume (e.g. 27 mm from back of barrel flange to back of plunger stopper, 1 ml-long syringe);

— characterization of entire barrel: Select a position corresponding to nominal fill volume (e.g. 10 mm from back of barrel flange to back of plunger stopper, 1 ml-long syringe).

E.4.2 Install the plunger rod into or onto the plunger stopper.

NOTE The plunger rod can be with or without thread.

E.4.3 Remove the needle shield or other front closure from the sterilized subassembled syringe ready for filling.

E.4.4 Place the sterilized subassembled syringe ready for filling in the adaptor plate on the force-measurement instrument.

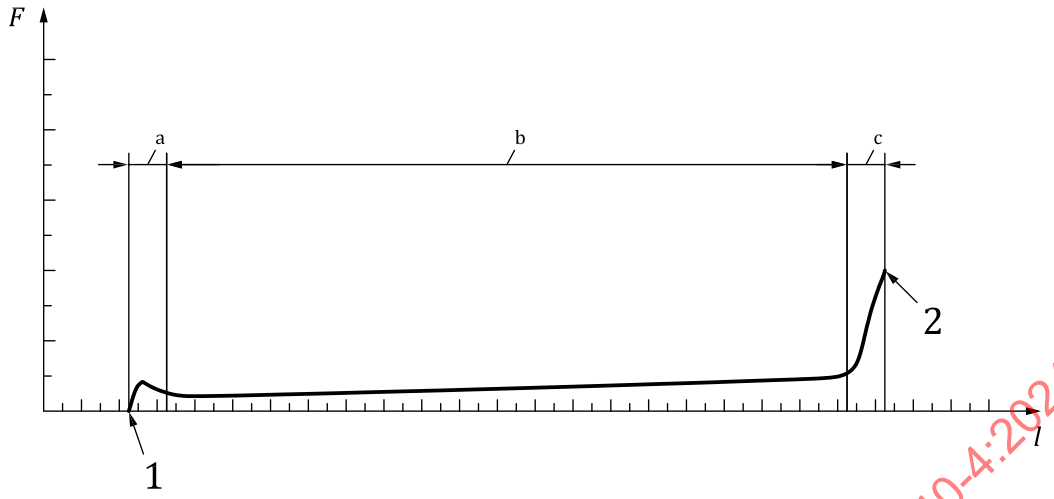
E.4.5 Start the compression at the designated speed.

E.4.6 End the test when the plunger stopper comes into contact with the shoulder of the syringe barrel.

E.4.7 Repeat the steps E.4.1 to E.4.6 for additional test samples.

E.4.8 Record the maximum force in the glide force test region. The glide force test region is as the region between the break loose until the sharp increase of the force at the end of the stroke. See Figure E.1.

Limit values should be agreed between the manufacturer and the customer.



Key

1 start of stopper movement
2 end of testing condition
F force in newton
l distance in millimetre
a Break loose region.
b Glide force test region.
c End of stroke region.

Figure E.1 — Example illustrating gliding characteristics

E.5 Test report or documentation

The test report or documentation should include the following:

— maximum gliding force in the glide force test region (b) (N);

— calculated average gliding force (N);

— numbers of tested samples;

— any deviations or observations.

NOTE If the software does not allow to print all setup parameters, traceability of all required parameters is given by additional documentation.

Annex F
(informative)

Needle penetration test

F.1 Principle

This test method is used to determine the needle penetration force by piercing a test foil with a needle. The test has been derived from DIN 13097-4[13].

NOTE Further information can be found in ISO 7864:2016, Annex D.

Whenever a test method requires a peak measurement, a higher sampling rate (in Hz) will result in a more accurate result. Therefore, a sampling rate of 500 Hz is recommended for such tests. For all other tests, a sampling rate of minimum 100 Hz is recommended.

F.2 Apparatus

F.2.1 Universal tensile and compression testing machine conforming with the following:

— measuring range up to 10 N or as appropriate;

— test speed within the range 20 mm/min to 200 mm/min or as appropriate.

NOTE The definitions of measuring range and test speed are subject to agreement between the manufacturer and the customer.

F.2.2 Needle holder.

F.3 Materials

F.3.1 Test foil, specification to be agreed upon between the manufacturer and the customer.

F.3.2 Needles and syringes with a staked needle as supplied or with pre-treatment, i.e. siliconized, in accordance with ISO 9626, numbers as appropriate, sample size to be agreed upon between the manufacturer and the customer.

NOTE Test is valid for syringe barrel as well as for sterile subassembled syringes ready for filling.

F.4 Procedure

F.4.1 Fix the test foil tension-free in the holder.

F.4.2 Fix the needle in the needle holder perpendicular to the test foil and with the tip to the geometric centre of the free area of the test foil.

F.4.3 Start the test and penetrate the test foil with the needle.

F.4.4 Record the force versus displacement curve.

F.4.5 Use a new (not perforated) foil section for each penetration test.

Examples on penetration force behaviour and force versus displacement curve are given in Figure F.1 and Figure F.2.

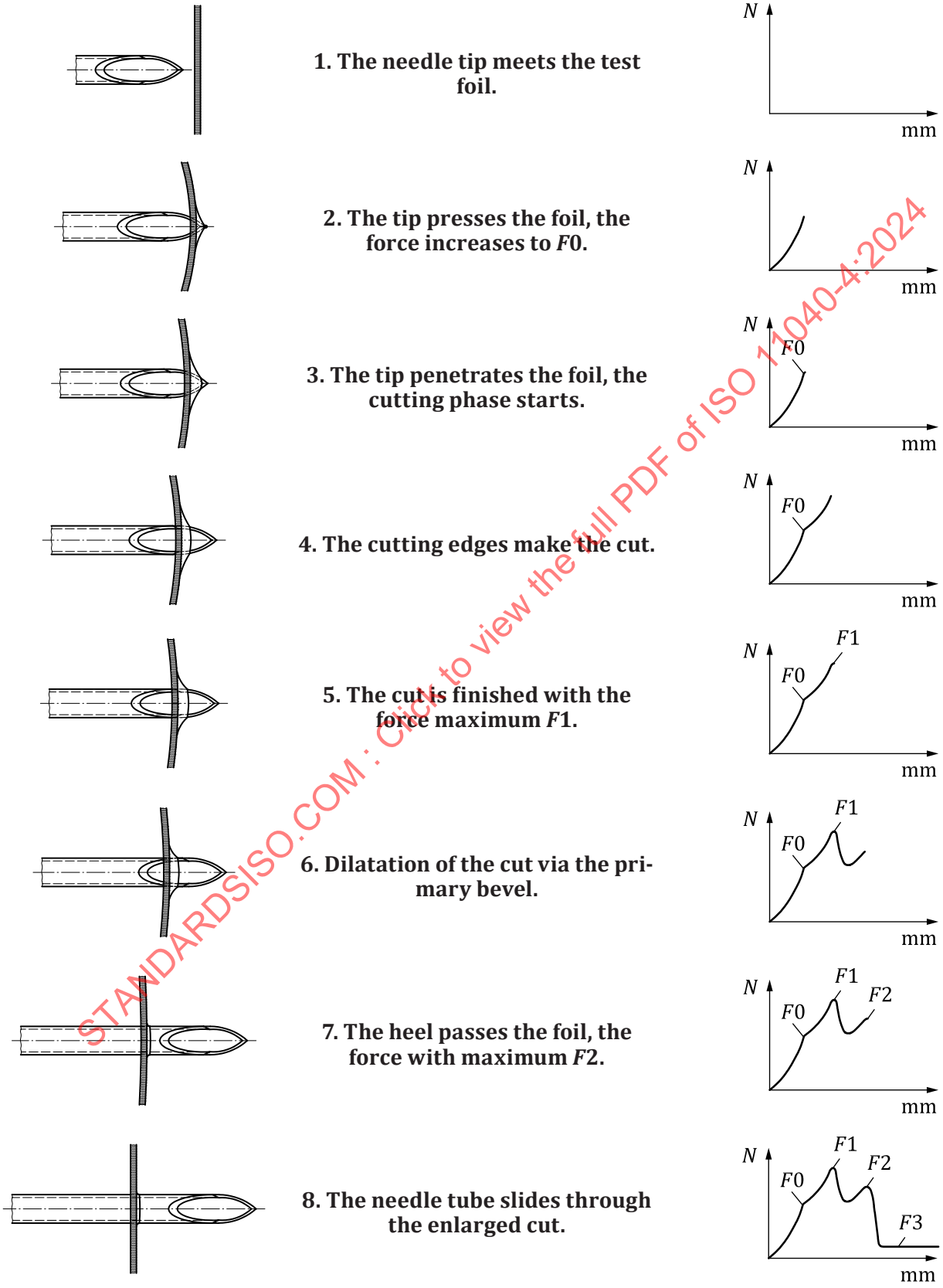
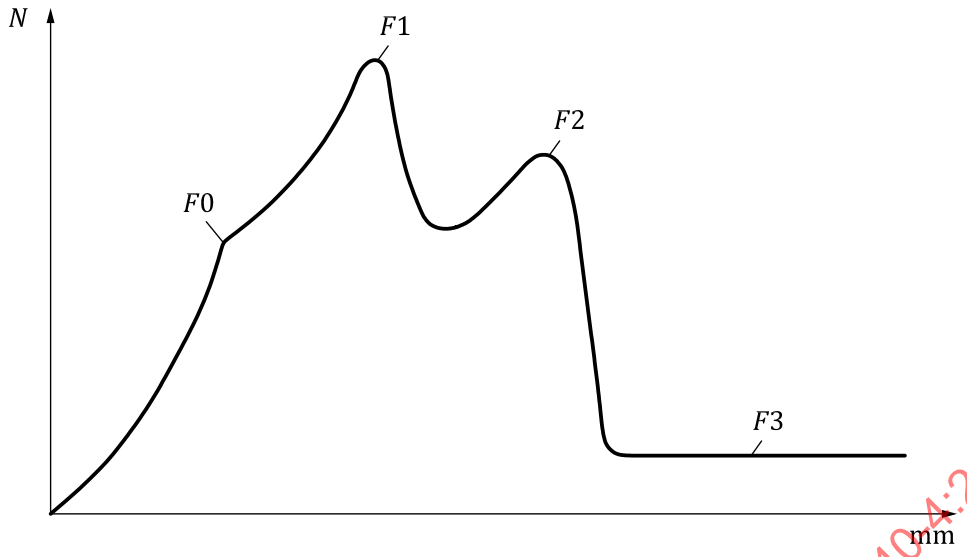


Figure F.1 — Stages of the penetration process



Key

*F*0 force for passing the tip (piercing force)

*F*1 force for cutting with the cutting edges (cutting force)

*F*2 force where the heel passes the foil

*F*3 drag penetration force

This curve is not representative of all needles and test foils.

Figure F.2 — Example of a force versus displacement curve

F.5 Test report or documentation

The test report or documentation should include the following:

— specification of the test foil;

— test speed (mm/min);

— force versus displacement curves;

— numbers of tested samples;

— any deviations or observations.

NOTE If the software does not allow to print all setup parameters, traceability of all required parameters is given by additional documentation.

Annex G
(normative)

Test methods for front end components

G.1 Needle pull-out force

G.1.1 Principle

The test is used to assess the fixation of the needle to the syringe.

It is mainly designed to verify whether the needle bonding process is appropriate to show that the staked needle withstands the pull-out force according to 6.5.2.6.

Whenever a test method requires a peak measurement, a higher sampling rate (in Hz) will result in a more accurate result. Therefore, a sampling rate of 500 Hz is recommended for such tests. For all other tests, a sampling rate of minimum 100 Hz is recommended.

G.1.2 Materials

G.1.2.1 Sterilized subassembled syringes ready for filling with a staked needle, numbers as required.

NOTE Test is valid for syringe barrel as well as for sterile subassembled syringes ready for filling.

G.1.3 Apparatus

G.1.3.1 Universal tensile and compression testing machine conforming with the following:

— load cell of max 500 N or as appropriate for the force to be measured;

— test speed of 50 mm/min or as appropriate.

NOTE The definitions of load cell, test speed, and sampling rate are subject to agreement between the manufacturer and the customer.

G.1.3.2 Syringe holder (syringe can be fixed by shoulder or finger flange during testing).

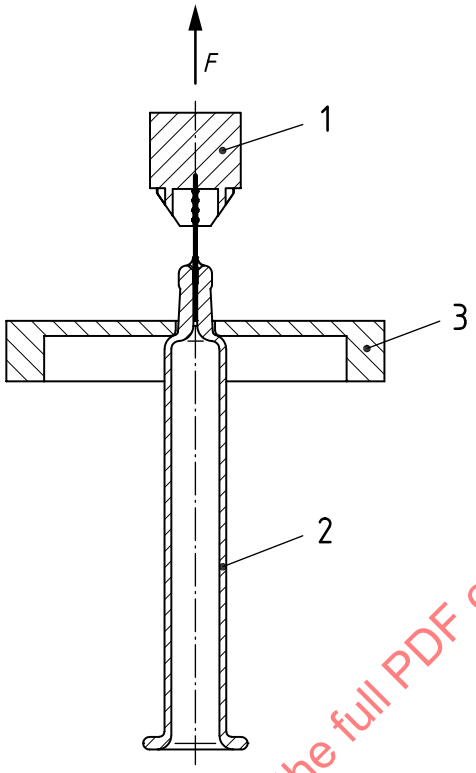
G.1.3.3 Needle gripper device, designed to avoid slippage and to avoid an influence on the measurement itself.

G.1.4 Preparation and preservation of test samples

The test samples shall follow the same process as the product delivered.

G.1.5 Procedure

G.1.5.1 Insert the test sample vertically positioned on the testing machine (see Figure G.1).



Key

1 needle gripper attached to a testing machine
2 syringe with staked needle
3 syringe holder/base plate
F force, in newtons

Figure G.1 — Position of the test sample in the tensile testing machine

G.1.5.2 Grip as much as possible of the needle to avoid slippage.

G.1.5.3 Release the test sample.

G.1.5.4 Set the load cell to "zero". No significant pre-load shall be applied when the "zero" is set.

G.1.5.5 Apply a test speed of 50 mm/min or as appropriate.

G.1.5.6 Start the test.

G.1.5.7 Record the force versus displacement.

G.1.5.8 Stop the test once the needle is clearly removed from the syringe or broken.

G.1.6 Expression of results

Record the maximum load peak from the force versus displacement curve. This corresponds to the pull-out force of the needle system as described in 6.5.2.6.

G.1.7 Test report or documentation

The test report or documentation shall include the following:

— test speed (mm/min);

— force versus displacement curve;

— peak value according to the maximum force (N);

— number of tested samples;

— any deviations or observations.

NOTE If software does not allow to print all setup parameters, traceability of all required parameters is given by additional documentation.

G.2 Syringe closure system liquid leakage test

G.2.1 Principle

The test is used to assess the liquid leakage resistance of the syringe closure systems (needle shield or tip cap) assembled onto the syringe.

It is mainly designed to verify whether the syringe closure system is able to withstand any potential overpressure inside the syringe during the filling process or during transportation.

The test pressure of 110 kPa has been selected based on process conditions during the fill finish process.

Whenever a test method requires a peak measurement a higher sampling rate (in Hz) will result in a more accurate result. Therefore, a sampling rate of 500 Hz is recommended for such tests. For all other tests, a sampling rate of minimum 100 Hz is recommended.

G.2.2 Reagents and materials

G.2.2.1 Reagents of recognized analytical grade and distilled water or water of equivalent purity.

G.2.2.2 Sterilized subassembled syringes, ready for filling, numbers as required.

NOTE Test is valid for syringe barrel as well as for sterile subassembled syringes ready for filling.

G.2.3 Apparatus

G.2.3.1 Universal tensile and compression testing machine or pressurization through the application of compressed air. Application of pressure via universal tensile and testing machine (see Figure G.2) is preferred when wall friction can be neglected. In this case, it is assumed that equilibrium is reached between the applied force and the internal pressure. If wall friction cannot be neglected, preference is given to the test as indicated in Figure G.2, where the pressures are applied on the syringe closure system through the application of compressed air on the filled media.

G.2.3.2 Syringe holder.

G.2.3.3 Plunger stopper/piston and plunger rod/piston rod.

G.2.4 Preparation and preservation of test samples

The retention time/waiting time between closure setting and leakage testing shall be at least 12 h. Do not damage and/or loosen the syringe closure system/syringe tip prior to testing.

G.2.5 Procedure

G.2.5.1 Insert the test sample into the holder. See Figure G.2.

G.2.5.2 Fill the test sample to between 1/3 and 2/3 of the nominal fill volume with the reagent (see G.2.2.1).

G.2.5.3 In case of pressurization, close the holder with the lid and secure the device.

G.2.5.4 Apply a pressure of 110 kPa and hold the pressure for 5 s.

The correlation between the test force and the cross-sectional area of the syringe that is determined by the nominal inner diameter of the syringe can be calculated using Formulae (G.1) to (G.3). Dimensions are based on Table 1.

from

$$F = p \times A \tag{G.1}$$

and

$$A = \frac{\pi}{4} \times d^2 \tag{G.2}$$

follows

$$F = p \times \frac{\pi}{4} \times d^2 \times 10^{-3} \tag{G.3}$$

where

F is the force in newton;

p is the target internal pressure, in kPa (i.e. 110 kPa);

A is the cross-sectional area of the syringe barrel, in mm^2;

d is the nominal inner diameter of the syringe barrel, in mm.

G.2.5.5 Release the pressure.

G.2.5.6 Monitor the test samples for leakage during and after the test.

G.2.6 Expression of results

The test is passed if the tip caps are not falling off and or if no droplets are visible around the external surfaces of the syringe closure system (wet surface of tip cap or needle shield) or both.

Visually examine if the test samples have passed or failed the test.

G.2.7 Test report or documentation

The test report or documentation shall include the following:

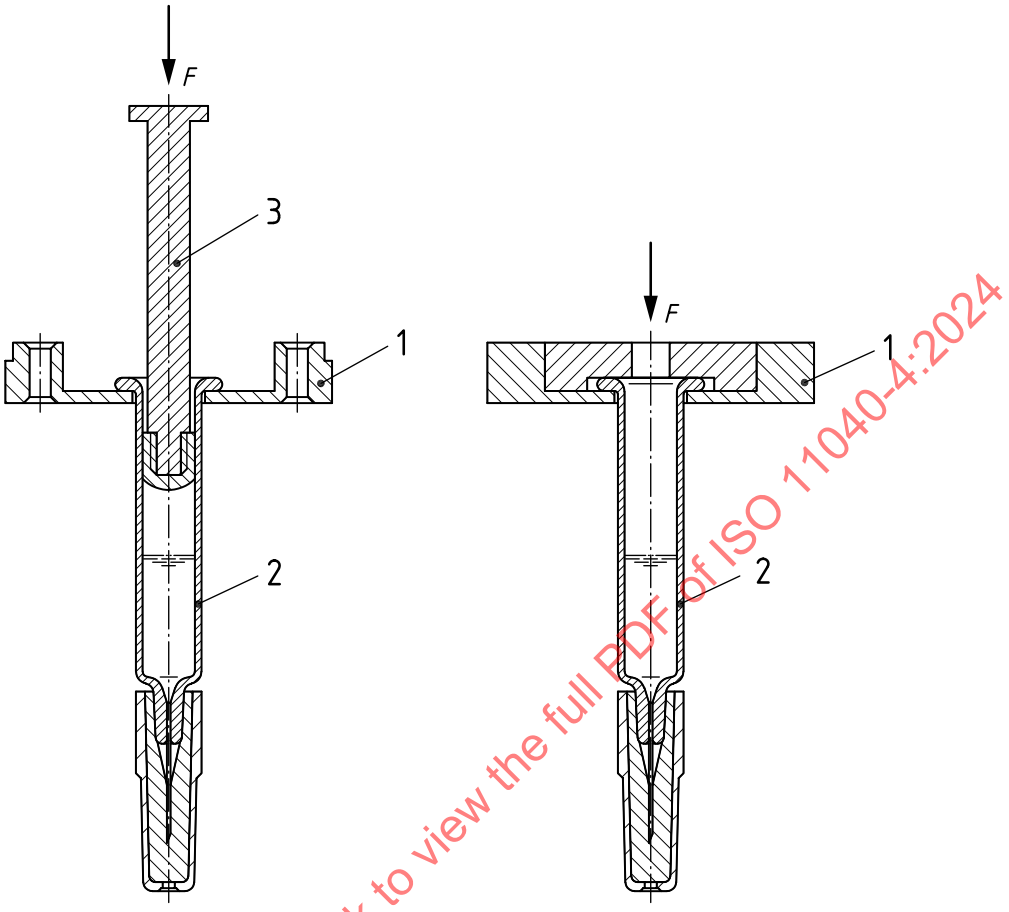
— applied pressure (kPa), or force (N);

— number of tested samples;

— number of passed/failed samples according to the specification as agreed between customer and manufacturer;

— any deviations or observations.

NOTE If the software does not allow to print all setup parameters, traceability of all required parameters is given by additional documentation.



Key

1 syringe holder

2 syringe with closure system

3 plunger rod/piston rod and plunger stopper/piston

F force, in newtons

This illustration includes a syringe with a needle shield as an example. The testing is equally applicable to syringes with a tip cap.

Figure G.2 — Examples of testing devices for the determination of syringe closure system liquid leakage

G.3 Luer lock adaptor collar pull-off force

G.3.1 Principle

The test is used to assess the pull-off force of a Luer lock adaptor (LLA) collar system of sterilized subassembled syringes ready for filling.

It is mainly designed to verify whether the LLA collar system is able to withstand an axial pull-off force in order to avoid detachment of the LLA collar system from the syringe barrel by the insertion of a socket 6 % (Luer) conical lock fitting.

Whenever a test method requires a peak measurement, a higher sampling rate (in Hz) will result in a more accurate result. Therefore, a sampling rate of 500 Hz is recommended for such tests. For all other tests, a sampling rate of minimum 100 Hz is recommended.

G.3.2 Materials

G.3.2.1 Sterilized subassembled syringes ready for filling with LLA, number as required.

NOTE Test is valid for syringe barrel as well as for sterile subassembled syringes ready for filling.

G.3.3 Apparatus

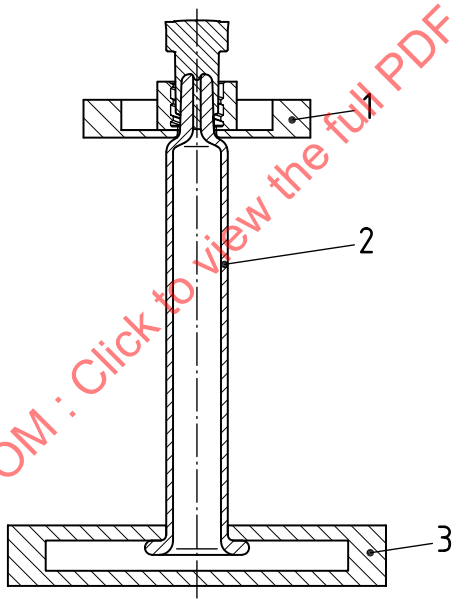
G.3.3.1 Universal tensile and compression testing machine conforming with the following:

— test speed of 20 mm/min or as appropriate (see ISO 80369-7);

— load cell appropriate to the force to be measured, typical range of load cell is between 10 N and 100 N.

NOTE The definitions of load cell and test speed are subject to agreement between the manufacturer and the customer.

G.3.3.2 Syringe holder and gripper device, see Figure G.3.



Key

1 LLA gripper plate
2 syringe with LLA/LLA systems
3 syringe holder/base plate

Figure G.3 — Example of a testing device for the determination of the Luer lock adapter collar pull-off force

G.3.4 Preparation and preservation of test samples

The test samples shall follow the same process as the product delivered.

G.3.5 Procedure

G.3.5.1 Remove the tip cap.

G.3.5.2 Insert the test sample vertically positioned on the testing machine between the holder (finger flange side) and the gripper (LLA collar side).

G.3.5.3 Make sure that no pressure/movement is applied to the LLA collar system during test assembling.

G.3.5.4 Release the test sample.

G.3.5.5 Set the load cell to "zero". No significant pre-load shall be applied when "zero" is set.

G.3.5.6 Apply a test speed of 20 mm/min or as appropriate.

G.3.5.7 Record the force versus displacement.

G.3.5.8 Stop the test once the LLA collar system is clearly removed from the syringe tip.

G.3.6 Expression of results

Determine the load peak from the force versus displacement curve. The peak value corresponds to the pull-off force of the LLA collar system of the syringe.

G.3.7 Test report or documentation

The test report or documentation shall include the following:

— test speed (mm/min);

— peak value (pull-off force) (N);

— number of tested samples;

— number of passed/failed samples according to specification;

— any deviations or observations.

NOTE If software does not allow to print all setup parameters, traceability of all required parameters is given by additional documentation.

G.4 Luer lock adaptor collar torque resistance

G.4.1 Principle

The test is used to assess the torque resistance of an LLA collar system of a sterilized subassembled syringe ready for filling.

It is mainly designed to verify whether the LLA collar system is able to withstand an applied torque while inserting a socket 6 % (Luer) conical lock fitting (i.e. needle hub).

Whenever a test method requires a peak measurement, a higher sampling rate (in Hz) will result in a more accurate result. Therefore, a sampling rate of 500 Hz is recommended for such tests. For all other tests a sampling rate of minimum 100 Hz is recommended.

G.4.2 Materials

G.4.2.1 Sterilized subassembled syringes ready for filling with LLA, number as required.

NOTE Test is valid for syringe barrel as well as for sterile subassembled syringes ready for filling.