INTERNATIONAL STANDARD

ISO 11040-4

Third edition
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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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Contents

Page

Foreword

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The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation on the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the WTO principles in the Technical Barriers to Trade (TBT) see the following URL: Foreword - Supplementary information

The committee responsible for this document is ISO/TC 76, *Transfusion, infusion and injection, and blood processing equipment for medical and pharmaceutical use*.

This third edition cancels and replaces the second edition (ISO 11040-4:2007), which has been technically revised and contains the following changes:

— Scope has been extended by adding sterilized subassembled syringes ready for filling and appropriate requirements, as well as test methods, have been included;

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

— requirements on labelling have been revised;

— requirements on packaging have been added;

— requirements on syringes barrels have been revised by

  — adding requirements and related test methods for flange breakage resistance and Luer cone breakage resistance,

  — adding requirements on lubrication,

  — adding requirements and guidance on tolerances for Luer conical fittings, as well as on functional testing of Luer connections, and

  — deleting the clause on designation.

ISO 11040 consists of the following parts, under the general title *Prefilled syringes*:

— *Part 1: Glass cylinders for dental local anaesthetic cartridges*

— *Part 2: Plunger stoppers for dental local anaesthetic cartridges*

— *Part 3: Seals for dental local anaesthetic cartridges*

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

— *Part 5: Plunger stoppers for injectables*

— *Part 6: Plastics barrels for injectables*

— *Part 7: Packaging systems for sterilized subassembled syringes ready for filling*

— *Part 8: Requirements and test methods for finished prefilled syringes*

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 has to 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 rubber plungers, tip caps, needle shields, and other 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 apply this part of ISO 11040 to achieve a degree of standardization in the equipment of the machines.

At the start 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 lubrication, sealing the syringe with a closure system, sterilization, as well as filling and closing, were then performed in the pharmaceutical companies. Processing of "bulkware" is performed like this until today. 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 cone 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 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 porous 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 part of ISO 11040 applies to

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

— sterilized subassembled syringes ready for filling.

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

This part of ISO 11040 also specifies those components that are part of the sterilized subassembled syringe ready for filling.

Glass barrels and sterilized subassembled syringes ready for filling in accordance with this part of ISO 11040 are intended for single use only.

Components to complete the subassembled syringe, such as plunger and rod, are not specified in this part of ISO 11040.

NOTE Attention is drawn to applicable national or regional regulations such as Ph. Eur., USP, or JP. Where relevant, specific references to Ph. Eur., USP, and JP have been given in specific clauses or subclauses of this part of ISO 11040.

2 Normative references

The following documents, in whole or in part, are normatively referenced in this document and are indispensable for its application. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 594-1,[1)] Conical fittings with a 6 % (Luer) taper for syringes, needles and certain other medical equipment — Part 1: General requirements

ISO 594-2,[1)] Conical fittings with 6 % (Luer) taper for syringes, needles and certain other medical equipment — Part 2: Lock fittings

ISO 720:1985, *Glass — Hydrolytic resistance of glass grains at 121 degrees 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, *Sterile hypodermic needles for single use*

ISO 7886-1:1993, *Sterile hypodermic syringes for single use — Part 1: Syringes for manual use*

1) ISO 594-1 and ISO 594-2 will be replaced by ISO 80369-7 (currently in preparation by ISO/TC 210).

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 devices*

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*

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

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
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

3.3
needle shield
syringe closure used with staked needle subassembled syringes that is designed to protect the needle point/bevel from damage, to allow sterilization of the needle, and to maintain sterility of the contents of the syringe and of the needle up to the time of injection

3.4
prefilled syringe
container system filled with the injectable product ready for injection

Note 1 to entry: Components of syringes are barrel, needle, closure system, plunger, and rod. Examples of sterilized subassembled syringes ready for filling including components are illustrated in Annex A.

3.5
syringe barrel
cylindrical glass body with front end and finger flange

Note 1 to entry: See Figure 1.

Note 2 to entry: The syringe barrel can be equipped with a staked needle.

3.6
sterilized subassembled syringe ready for filling
subassembly that has been pre-treated, consisting of a syringe barrel and a closure system

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

— assembling/lubricating a needle;

— final washing/pyrogen reduction;

— drying;

— applying lubricant to the inner surface;

— sealing the syringe with a closure system;

— 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.

3.7
syringe closure system
component or multi-component system designed to close the syringe system at the front end that is designed to allow sterilization of the glass tip and maintain sterility of the contents of the syringe up to the time of injection

EXAMPLE Tip cap, needle shield, tamper-evident closure system.

Note 1 to entry: See 3.3.

3.8
user
patient or health care provider (clinical personnel, doctor, or lay person) who uses or applies the injectable product contained in the syringe

4 General requirements

4.1 Quality systems

The activities described within this part of ISO 11040 shall be carried out within a formal quality system.

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

4.2 Testing

4.2.1 Any suitable test system can be used when the required accuracy (calibration) and precision (gauge repeatability and reproducibility) can be obtained. The gauge repeatability and reproducibility of the test apparatus shall be no greater than 20 % of the allowed tolerance range for any given measurement. For destructive test measurements, the gauge repeatability and reproducibility shall be no greater than 30 % of the allowed tolerance range. At a minimum, the gauge repeatability and reproducibility should cover ±2 standard deviations (thereby covering approximately 95 % of the variation).

EXAMPLE A measurement system with a measurement specification limit of ±0,01 ml (range of 0,02 ml) comes out of the gauge repeatability and reproducibility with a gauge repeatability and reproducibility/tolerance range ratio of 20 %, which means that the gauge repeatability and reproducibility (four standard uncertainties) equals 0,02 ml/5 = 0,004 ml. The uncertainty of the measurement is ±2 standard deviations (see Reference [22]), which equals to 0,002 ml.

4.2.2 The sampling plans used for the selection and testing of sterilized subassembled syringes ready for filling or components thereof shall be based upon statistically valid rationale.

NOTE Examples of suitable sampling plans are given in ISO 2859-1 and ISO 3951- series; see also Reference [25].

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

4.3 Documentation

4.3.1 Demonstration of compliance with the requirements of this part of ISO 11040 shall be documented.

4.3.2 All documentation shall be retained for a specified period of time. The retention period shall consider factors such as regulatory requirements, expiration date, and traceability.

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

4.3.4 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 reliable.

5 Syringe barrel

5.1 Design including dimensions

5.1.1 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 that are given for information only.

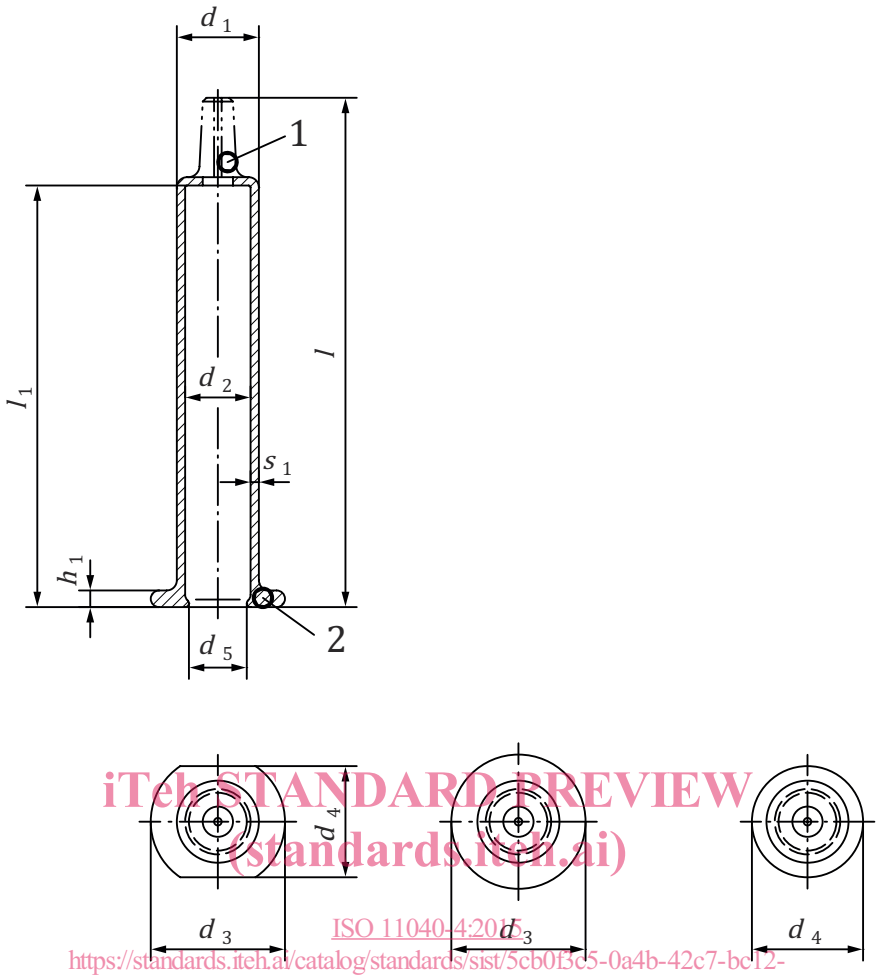
The type of head design shall be agreed upon between the manufacturer and the customer. For the Luer and the Luer lock design, ISO 594-1, ISO 594-2, and ISO 80369-1 apply, with the addition that the dimension of the Luer conical fitting shall comply with Figure 2.

NOTE Commercially developed glass Luer cone and Luer lock prefilled syringes routinely mate with Luer devices in order to effectively administer the medication stored within the syringe. Examples are disposable needles, needleless connector devices, and other forms of Luer access. The current state of the art syringe tip glass forming technology for manufacturing glass prefilled syringes cannot conform completely to the standards on Luer connectors (see ISO 594 series). The ISO 594 series has been developed using ground glass, metal, and injection moulded technology, as well as plastic resins, as the baseline rationale for compliance and capabilities.

Differences in the manufacturing methodologies and the need for expanded tolerances in the glass forming manufacturing process are acknowledged. This is why dimensional tolerances are different. While these tolerances are outside of the range of ISO 594 with respect to some of the dimensions, the glass formed tip does successfully mate with the injection moulded female counterparts. See 5.2 and ISO 594:1986 for functional test methods that accommodate for the formed tip manufacturing process.

Luer tip dimensions mentioned in the following figures can be checked by means of camera measurements or indirectly by using a gauge similar to the one described in ISO 594.

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



a) cut-flange b) round flange c) small-round flange

Key

1 front end

2 back end

NOTE 1 The bore diameter of the tip is subject to agreement between the manufacturer and the customer. For examples of commonly used head designs, see Annex B.

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

Figure 1 — Typical example of a glass syringe barrel and examples of glass finger flanges

Table 1 — Syringe barrel dimensions (see Figure 1)

Dimensions in millimetres

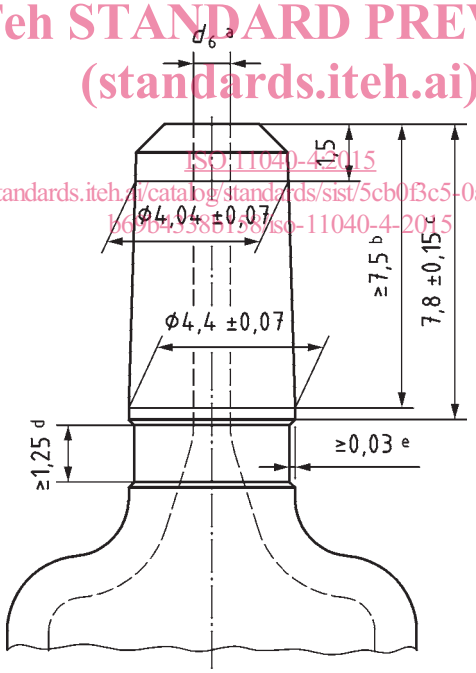
Nominal volume	Glass barrel										Finger flange					
	d_1		d_2		d_5	l_1		l^c		$s_1{}^c$	h_1		d_3		d_4	
ml	nom	tol	nom	tol	min.	nom.	tol.	nom.	tol.	≈	nom.	tol.	nom.	nom.	nom.	tol.
0,5	6,85		4,65	±0,1	4,40	47,6		57,5		1,1	1,8	±0,5	13,4	±0,4	10,5	±0,4
1[a]	8,15		6,35		6,05	54		64,0	±0,5	0,9	1,9		13,8		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	
2	10,85		8,65		8,25	49		60,0		1,1	2,2		17,75	±0,75	14,7	
2,25	10,85		8,65		8,25	54,4		66,6	±0,75	1,1	2,2	±0,5	17,75		14,7	±0,5
3	10,85		8,65	±0,2	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/standard version.

[c] Dimension on total barrel length and wall thickness are for information only.

Dimensions in millimetres



Key

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

b Luer cone length, Luer version.

c Luer cone length, Luer lock version.

d Length of the Luer lock groove.

e Depth of the Luer lock groove.

NOTE The above dimensions are not applicable to glass barrel tip designs with a staked needle.

Figure 2 — Luer conical fitting

5.2 Functional testing of Luer connection

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

NOTE The forming process of glass prefillable syringes results 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, male Luer connectors of glass prefillable syringes 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, the plastic reference connectors shall be verified for compliance with the dimensional requirements of ISO 594-1.

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

5.3 Material

The material shall be colourless (cl) or amber (br) glass of the hydrolytic resistance grain class HGA 1 in accordance with ISO 720:1985.

Material requirements are also covered by national or regional pharmacopoeias. See requirements for glass type I as given in Ph. Eur. 3.2.1[32], USP <660>[39] and requirements in JP 7.01[47].

5.4 Performance requirements

5.4.1 Hydrolytic resistance

When tested in accordance with ISO 4802-1 or ISO 4802-2, the hydrolytic resistance of the internal surface of the glass barrel shall comply with the requirements of hydrolytic resistance container class ISO 4802-HC 1.

Before conducting the test, the back end of the barrel shall be sealed with a suitable closure element, e.g. a rubber closure.

5.4.2 Annealing quality

The maximum residual stress shall not produce an optical retardation exceeding 40 nm/mm of glass thickness when the glass 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 barrels whose inner surfaces have been lubricated, 6.5.1.2 applies.

5.4.4 Flange breakage resistance

Syringe barrels shall provide an appropriate flange breakage resistance. Limit values are subject to agreement between the manufacturer and the customer.

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

NOTE The flange breakage resistance test method is a reference test to provide a consistent measure for comparison of the performance of different syringes and can potentially be used as a quality measure to assess changes and monitor production. The test method might need to be adjusted to simulate specific use conditions of the syringe system, e.g. use in auto-injectors.

5.4.5 Luer cone breakage resistance

Syringe barrels shall provide an appropriate Luer cone breakage resistance. Limit values are subject to agreement between the manufacturer and the customer.

The Luer cone breakage resistance shall be determined in accordance with C.2.

NOTE The Luer cone breakage resistance test method is a reference test to provide a consistent measure for comparison of the performance of different syringes and can potentially be used as a quality measure to assess changes and monitor production. The test method might need to be adjusted to simulate specific use conditions of the syringe system, e.g. use in auto-injectors.

6 Sterilized subassembled syringes ready for filling

6.1 General

6.1.1 The design of sterilized subassembled syringes ready for filling varies due to their intended use. The requirements and test methods in the following subclauses and related annexes are based on common design features and syringe components.

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

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

a) microbial barrier;

b) biocompatibility and toxicological attributes;

c) physical and chemical properties;

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

e) maintenance of sterility of the subassembly;

f) shelf-life limitations;

g) functionality for their intended use;

h) robustness of the closure system during transport from the manufacturer to the user.

6.1.3 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 suitable 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 11135-1, ISO 17665-1, ISO 11137, 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. Sterility testing is subject of national or regional pharmacopoeias. See the methods given in Ph Eur, 2.6.1[27], USP <71>[34] and JP 4.06[44].

For ethylene oxide sterilization, the requirements for residuals of ISO 10993-7 apply. See also Reference [26].

NOTE See also other applicable parts of ISO 10993.

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.

NOTE 1 For rationale, see USP monograph on sterile water for injection according to USP <1231>[41].

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

— for extraction method, see USP <161>[37];

— for testing, see Ph Eur, 2.6.14, method c)[28], USP <85>[35] and JP 4.01[43].

NOTE 2 A sample preparation 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 Particles

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

Current pharmacopoeias identify visible particulates as undesirable but do not define the size or put a limit on the allowable number. It is recommended that the manufacturer and the customer 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.

For sub-visible particles, the following applies:

— 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>[40] (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>[40], supports the customer to fulfil the USP requirements on the syringe system. This value has been chosen based on historical proven capability using the light obscuration method as given in D.2.

NOTE 2 See also Ph. Eur. 2.9.19 [29], Ph. Eur. 2.9.20 [30], USP <788>[40], JP 6.06[45], as well as JP 6.07[46].

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

6.5.1 Barrel

6.5.1.1 The requirements given in Clause 5 apply.

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

6.5.1.2 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.

