Guideline for Prefilled Syringes

This guideline applies to sterile prefilled syringes packaging system for pharmaceutical packaging that are packaged in nest tubs. Non-sterile prefilled syringes for pharmaceutical packaging can refer to this guideline.

In terms of syringe barrel material, it is classified as glass prefilled syringes and plastic prefilled syringes. The glass barrel is mainly made of borosilicate glass, and the common plastic barrel materials are cyclic olefin (e.g. cyclopentene, norbornene) polymer (COP), cyclic olefin (e.g. cyclopentene, norbornene) and olefins (e.g. ethylene or propylene) copolymer (COC) and polypropylene (PP).

In terms of the form of the front end of the syringe, it is classified as prefilled syringes with staked needle and prefilled syringes without staked needles. In addition, prefilled syringes without staked needle can be classified as prefilled syringes with Luer cone and prefilled syringes with Luer lock cone according to Luer cone type at the front end.

1 Terms and definitions

1.1 Syringe barrel

Cylindrical glass or plastic body with front end (Luer conical fitting or staked needle) and finger flange as back end.

1.2 Syringe barrel with staked needle

Barrel with a staked needle front end. The needle can be fixed by inserting molding, gluing, or other bonding methods.

1.3 Syringe barrel with Luer conical fitting

Barrel with a Luer conical fitting front end.

1.4 Tip cap/needle shield

Component or multi-component systems designed to close the syringe system at the front end that is designed to allow the sterilization of cone or staked needle and maintain sterility of the contents of the syringe up to the time of injection, such as tip cap, needle shield. According to the connection type with the barrel, it can be divided into locked tip cap/needle shield and unlocked tip cap/needle shield.

1.5 Subassembled prefilled syringes

Packaging components that have been sterilized, consisting of a barrel and a tip cap/needle shield.

1.6 Prefilled syringes

A container system used for filling the injectable product ready for injection, the components of which include subassembled prefilled syringe, plunger stopper, plunger rod, and booster (if any).

2 Requirements

2.1 Production requirements

The production of the components of prefilled syringes shall comply with relevant

good manufacturing practices to ensure that the products meet pharmaceutical requirements. If it is necessary to spray silicone oil on the inner surfaces of the syringe barrel to improve gliding properties, the silicone oil shall comply with pharmaceutical requirements. For prefilled syringes with staked needle, when selecting stainless steel needles, attention shall be paid to information regarding the raw material's rigidity, toughness, and corrosion resistance. If it is necessary to treat the needle surface with a lubricant (e.g., silicone oil), the silicone oil shall meet pharmaceutical requirements, and the penetration force of the needle shall be evaluated comprehensively based on clinical usage conditions. Sterilization shall be carried out using a suitable validated method to achieve a Sterility Assurance Level of 10^{-6}, and it must guarantee the product remains sterile throughout its shelf life. If it is claimed that the protective bag can maintain the sterility of the product during its shelf life, its sterility retention capacity shall be evaluated. For plastic prefilled syringes, special focus shall be given to the impact of the sterilization process on the colour and transparency of the syringe barrel. The compatibility of the nest and tub sizes with the filling equipment of the drug manufacturer needs to be considered.

2.2 Application requirements

Drug manufacturers shall select and use appropriate prefilled syringes based on risk assessment to ensure the quality and safety of drug products. Products shall be selected based on specifications and dimensions that comply with the enterprise specification or quality agreements to avoid affecting the compatibility between components and the sealability of the container system, and the evaluation can be carried out with reference to Guideline for Closure Integrity of Sterile Pharmaceutical Packaging Systems (Guideline 9628) by selecting appropriate methods (e.g., physical, microbiological). Verification of the accuracy of graduation markings or indicator lines on the syringe barrel (such as pre-printed or on labels) is required to ensure they meet the intended use requirements. For products that undergo terminal sterilization, attention shall be paid to the effects of re-sterilization on various components of the pre-filled syringe, such as the sealability between components. Attention needs to be given to the risks of microbial contamination and/or particulate contamination to the pharmaceutical production environment posed by the pre-filled syringe and its outer packaging system, as well as the impact of silicone oil residues and tungsten residues in glass barrels on the drug.

Drug manufacturers need to pay attention to the impact of drugs on the intended performance of pre-filled syringes, such as ensuring the smoothness and effectiveness of drug delivery for high-viscosity drugs. If the product is intended to be used in combination with preattached, copackaged or label referenced device and equipment, the drug manufacturer shall ensure that the whole combination product, including the connection system, is safe and usable.

2.3 Biological evaluation

Refer to Guideline on Biological Evaluation and Test Selection of Pharmaceutical Packaging Materials (Guideline 9629) to evaluate the biological safety of prefilled syringes.

2.4 Component and material requirements

2.4.1 The plunger stopper and Tip cap/needle shield

Refer to the requirements for quality control in section 3 of the Guideline for Rubber Closures for Pharmaceutical Packages (Guideline 9623), and when applicable,

the requirements for bioburden, sterility, bacterial endotoxins or pyrogens in Annex 1 of the Guideline for Rubber Closures for Pharmaceutical Packages (Guideline 9623), to perform quality control on the plunger stopper and the tip cap/needle shield.

2.4.2 Stainless steel needle

Refer to the requirements for materials in section 3.1 of the Guideline for Metal Components for Pharmaceutical Packaging (Guideline 9625) for quality control of elemental composition.

2.4.3 Syringe barrel

Refer to the requirements in Annex 4 of the Guideline on Glass Containers for Pharmaceutical Packaging (Guideline 9622) for quality control of glass barrels.

Refer to the requirements for product quality control in section 3 of the Guideline for Plastic Packaging Systems and Components for Pharmaceutical Use (Guideline 9624) for quality control of plastic barrels.

3 Product quality control

With the purpose of ensuring the controllable quality of drugs, meeting clinical needs and safety in use, manufacturers and users of the prefilled syringes shall choose appropriate quality control items according to the real situation of production and use, and develop the enterprise specification or quality agreements. In addition to meeting the requirements for components and materials in 3.4, the prefilled syringes shall also meet the following requirements.

3.1 Subassembled prefilled syringes

3.1.1 Appearance

It is used to evaluate the appearance quality of the product. In bright natural light, visually inspect the appearance of the product in front of the eye, the result shall comply with the enterprise specification or quality agreements.

3.1.2 Luer conical fitting

It is used to evaluate the adaptability and clinical safety of the Luer conical fitting for subassembled prefilled syringes without staked needle.

3.1.2.1 General Requirements

Test according to the Examination Method of Luer Conical Fitting of Prefilled Syringes (General Chapter 4040), and the result shall comply with the requirements.

3.1.2.2 Luer lock adaptor collar pull-off force

It is used to evaluate the connection strength of the non-integrity Luer lock adaptor collar. Test according to the Determination of Bond Performance for Luer Lock Adaptor Collar of Prefilled Syringes (General Chapter 4043 method 2), the adaptor collar shall withstand a pull-off force of at least 22N to avoid detachment from the syringe barrel.

3.1.2.3 Luer lock adapter collar torque resistance

It is used to evaluate the torque resistance of the non-integrity Luer lock adaptor collar. Test according to the Determination of Bond Performance for Luer Lock Adaptor Collar of Prefilled Syringes (General Chapter 4043 method 1), the result shall comply

with the enterprise specification or quality agreements.

3.1.3 Needle

It is used to evaluate the clinical safety and related performances of the needle for subassembled prefilled syringes with staked needle.

3.1.3.1 Bonding strength

Fix the syringe barrel, conduct a non-impact pull test on the needle in the direction of needle extraction under a load of 22N, the needle and the syringe barrel shall not be loose or detached.

3.1.3.2 Needle lumen patency

Evaluate according to one of the following methods, and the needle lumen shall be patency. If there are other specifications of needles, corresponding evaluation methods for needle lumen patency can be developed referring to this guideline.

a) A stainless steel stylet of the appropriate diameter selected from the diameters given in Table 1 shall pass through the needle;

b) The flow rate of water through the needle shall not be less than 80% of the needle of equivalent out diameter and length having a minimum inner diameter given in Table 2, when tested under the same water pressure of no more than 100kPa.

Table 1 Diameter of stylet

Unit: mm

Designated metric size of needle	Outer diameter of stylet $^{0}_{0.01}$	
	for needle of regular walled tubing	for needle of thin-walled tubing
0.30	0.11	0.13
0.33	0.11	0.15
0.36	0.11	0.15
0.40	0.15	0.19
0.45	0.18	0.23
0.50	0.18	0.23

Table 2 Size of needle

Unit: mm

Designated metric size (Gauge)	Outer diameter		Minimum Inner Diameter	
	minimum	maximum	regular wall	thin wall
0.30（30G）	0.298	0.320	0.133	0.165
0.33（29G）	0.324	0.351	0.133	0.190
0.36（28G）	0.349	0.370	0.133	0.190
0.40（27G）	0.400	0.420	0.184	0.241
0.45（26G）	0.440	0.470	0.232	0.292

0.50（25G）	0.500	0.530	0.232	0.292

3.1.4 Tip cap/needle shield

3.1.4.1 Sealability between tip cap/needle shield and barrel

Test according to the Examination Method of Sealability for Components of Prefilled Syringes (General Chapter 4041 method 1), the caps are not falling off and no droplets are visible around the external surfaces of the tip cap/needle shield.

3.1.4.2 Pull-off force

It is used to evaluate the compatibility between the unlocked protective cap and barrel. Test according to the Determination of Opening Performance for Tip Cap/Needle Shield of Prefilled Syringes (General Chapter 4042 method 1), and the result shall comply with the enterprise specification or quality agreements.

3.1.4.3 Luer lock semi-rigid tip cap unscrewing torque

It is used to evaluate the compatibility between the Luer lock tip cap and barrel. Test according to the Determination of Opening Performance for Tip Cap/Needle Shield of Prefilled Syringes (General Chapter 4042 method 2), and the result shall comply with the enterprise specification or quality agreements.

3.1.5 Silicone oil content

It is used to evaluate the amount of silicone oil sprayed on the inner surface of the syringe barrel. Test according to the Determination of Silicone Oil Content for Prefilled Syringes (General Chapter 4227), and the result shall comply with the enterprise specification or quality agreements.

3.1.6 Particulate matter

Test according to the Determination of Particulate Matter for Pharmaceutical Packaging Materials and Containers (General Chapter 4206), and the result shall comply with the enterprise specification or quality agreements.

3.1.7 Residual ethylene oxide

It is used to evaluate the amount of residual sterilant in products sterilized with ethylene oxide. If ethylene oxide is used for sterilization, it is necessary to consider the risks posed by ethylene oxide to patients and its impact on drugs. For example, test according to the Determination of Ethylene Oxide for Pharmaceutical Packaging Materials and Containers (General Chapter 4209), and the residual amount of ethylene oxide in each sample shall be less than 5μg.

3.1.8 Bacterial endotoxin

Prepare the test solution based on the container type specified in the Guideline for the Application of Bacterial Endotoxin Test (Guideline 9251) using plunger stoppers that are free of bacterial endotoxin or specified in the enterprise specification or quality agreements. Then test according to Test for Bacterial Endotoxin (General Chapter 1143), and the result shall comply with the enterprise specification or quality agreements.

3.1.9 Sterility

Refer to the Guideline on Microbiological Testing of Pharmaceutical Packaging

Materials (Guideline 9627) for sterility test, which shall be sterile.

3.1.10 Residual tungsten (if applicable).

It is used to evaluate the extractable tungsten for glass prefilled syringes. Test according to the Determination of Extractable Tungsten for Prefilled Syringes (General Chapter 4226), and the result shall comply with the enterprise specification or quality agreements.

3.2 Prefilled syringes

3.2.1 Compatibility between plunger stopper and plunger rod

Install the plunger rod into or onto the plunger stopper, fully insert the plunger stopper into the prefilled syringe filled with half of labelled quantity of water, expel the air, attach the protective cap, and slowly withdraw back about 3 mm. The plunger rod shall remain stable and not separate from the plunger stopper.

3.2.2 Sealability between plunger stopper and plunger rod

Test according to the Examination Method of Sealability for Components of Prefilled Syringes (General Chapter 4041, method 2), there shall be no liquid leakage through the plunger stopper.

3.2.3 Gliding properties

Install the plunger rod and plunger stopper into the syringe barrel, then fix the syringe barrel on the tensile testing machine. Push the plunger rod at a speed of 100mm/min±5mm/min or other suitable speed, the initial gliding force and the average gliding force shall comply with the enterprise specification or quality agreements.

3.2.4 Residual volume

Take a suitable number of the products, weigh the mass of the empty prefilled syringe using a balance with an accuracy of 0.1mg (W_0), inhale the labelled quantity of water with a temperature of 20□±5□, carefully expel all the air bubbles, wipe dry the outer surface of the prefilled syringe, and push the plunger stopper to remove the water (without draining the liquid in the needle or cone). Re-weigh the prefilled syringe (W_1), W_1-W_0 is the residual volume, which shall comply with the enterprise specification or quality agreements.

起草单位：山东省医疗器械和药品包装检验研究院　　联系电话：0531-82682912
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