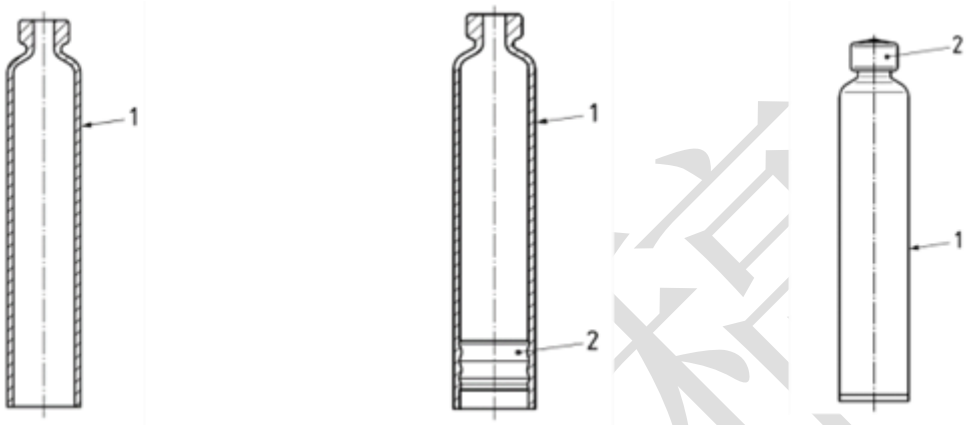
Guideline of Cartridge Systems for Pen-injectors

This guideline applies to single-chamber cartridge systems with glass barrels. Cartridge systems with barrels made of other materials or dual chamber cartridge systems can refer to this guideline.

The barrels of cartridge systems for pen-injectors can be divided into sterile packaging barrels and non-sterile packaging barrels. The barrels of sterile packaging usually include the following three formats, while the non-sterile packaging barrels are usually supplied in single-barrel format.



a) Sterile barrel **b) Preplungered sterile barrel** **c) Precapped sterile barrel**

Key: 1 barrel 2 plunger stopper 3 cap with disc

1 Terms and definitions

Pen-injectors An injection system typically consisting of a pen cap, pen holder, screw rod, pen body, dose adjustment plug and injection button is intended to be used in conjunction with needles and containers for injecting parenteral drugs.

Cartridge Systems for Pen-injectors Container systems for filling injectable drugs used in combination with pen-injector, consist of barrels, plunger stoppers, discs and caps (i.e. aluminum caps).

2 Requirements

2.1 Production requirements

The production of the components of cartridge systems for pen-injector shall comply with relevant general chapters for each material to ensure the products meet the pharmaceutical requirements. Meanwhile, special focus shall be given to the intended assembled pen-injector to ensure that the combination with the pen-injector is safe and compatible. For the production of sterile supplied components, special focus shall be given to the following content:

2.1.1 If pharmaceutical packaging material and container manufacturers need to siliconize the inner surface of barrels to improve gliding properties, special focus shall be given to its impact on drug quality.

2.1.2 Sterile-supplied components shall be sterilized using a suitable validated method to achieve a Sterility Assurance Level of 10^{-6}, while ensuring that the sterilization process does not affect the safety and performance of the components. The packaging

system shall ensure the product sterility within its expected and specified period.

2.1.3 Sterile supplied protective bags can protect products from external contamination like dust or dirt. If it is claimed that the protective bags can maintain product sterility within the expected period, its sterility retention capacity shall be evaluated.

2.1.4 For sterile components packaged in nest tubs, it is necessary to consider the compatibility between the size of the nest and tub and the filling equipment of pharmaceutical manufacturers.

2.2 Application requirements

Drug manufacturers shall select and use cartridge systems through risk assessment to ensure the quality and safety of drugs.

2.2.1 Special focus shall be given to the critical dimensions of each component avoid affecting the compatibility between components and closure integrity of the container system.

2.2.2 If drug manufacturers need to siliconize the inner surface of barrels to improve gliding properties, special focus shall be given to its impact on drug quality.

2.2.3 The evaluation can be carried out by selecting appropriate methods (e.g., physical, microbiological) referring to Guideline for Closure Integrity of Pharmaceutical Packaging Systems (Guideline 9650).

2.2.4 Bioburden control for non-sterile components can be conducted according to Guideline for Microbiological Test of Pharmaceutical Packaging Materials and Containers (Guideline 9653) to instruct the sterilization of products.

2.2.5 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.

2.2.6 Special focus shall be given to the impact of drugs on the expected performance of cartridge systems for pen-injectors, such as the smoothness and effectiveness of drug delivery for high-viscosity drugs.

2.3 Biological evaluation

The biological safety of cartridge systems for pen-injector can be evaluated by referring to Guideline for Biological Evaluation and Test Selection of Pharmaceutical Packaging Materials and Containers (Guideline 9651).

2.4 Components and materials

The discs and plunger stoppers of cartridge systems for pen-injectors shall comply with Section 5 of General Chapter of Rubber Closures for Pharmaceutical Packages (General Chapter 5200), as well as the requirements for particulate matter, bioburden, sterility, bacterial endotoxin, or pyrogens in General Chapter of Rubber Closures for Packages for Injections (General Chapter 5201), when applicable.

The glass barrels and glass beads of cartridge systems for pen-injectors shall comply with General Chapter on Glass Components for Pen-injector (General Chapter 5105).

3 Quality control

With the purpose of ensuring the controllable quality of drugs, meeting clinical needs and safety of use, manufacturers and users of cartridge systems and its components for pen-injectors shall choose appropriate quality control items (on the basis of meeting the requirements of 2.4 components and materials, including but not limited to the following requirements) according to the real situation of production and use, and develop the enterprise specification or quality agreements and develop inspection rules according to the risk management requirements of production and use.

3.1 Performance of seals

Seals shall be tested after sterilization according to expected sterilization method.

3.1.1 Sealability between disc/plunger stopper and barrel

This clause is used to evaluate resistance to liquid leakage of the seals of the cartridge system. Take cartridge barrels assembled with plunger stoppers/caps with discs, fill them with water of labelled quantity, then seal them with caps with discs/plunger stoppers. Make sure the samples are as air free as possible. Place the sample in a cartridge holder. Apply a force *F* calculated in accordance with formula (1) to the plunger stoppers for 1 minute. Check for leakage at the seals, which shall comply with the enterprise specification or quality agreements.

$$F = 0.64 \times d^2 \qquad (1)$$

Where F is the force to be applied, N;

d is the inner diameter of the glass barrel, mm;

0.64 is the correction factor, N/mm^2.

NOTE: Products filled with drugs can be used to do the test directly.

3.1.2 Resealability

This clause is used to evaluate resistance to liquid leakage for multi-dose products. Take cartridge barrels assembled with plunger stoppers /caps with discs, fill them with water of labelled quantity, then seal them with caps with discs/plunger stoppers. Make sure the samples are as air free as possible. Place the sample into a supporting pen-injector. Use a specified needle with the largest outer diameter of designated specification (if not designated, use a hypodermic needle with an outside diameter of 0.33mm) for the pen-injector to penetrate the center of the disc vertically in a manner consistent with its intended use. The penetration should be performed for at least the maximum number of intended use. Use a new needle for each puncture. After completing the penetration, take the sample out and place it in a cartridge holder. Apply a force *F* calculated in accordance with formula (2) to the plunger stoppers for 1min. Check for leakage at the disc, which shall comply with the enterprise specification or quality agreements.

$$F = 0.106 \times d^2 \qquad (2)$$

Where F is the force to be applied, N;

d is the inner diameter of the glass barrel, mm;

0.106 is the correction factor, N/mm^2.

NOTE: Products filled with drugs can be used to do the test directly.

3.1.3 Fragmentation

Take an appropriate amount of samples, the number of test samples shall permit a minimum of 100 puncture, the minimum sample number is 5 (for example, if each disc

is to be punctured 10 times, select at minimum 10 test samples; if each disc is to be punctured 20 times, select 5 test samples). Fill the cartridge barrels assembled with plunger stoppers/caps with discs with water of labelled quantity, then seal them with caps with discs/plunger stoppers. Place the sample into a supporting pen-injector. Use a specified needle with the largest outer diameter of designated specification (if not designated, use a hypodermic needle with an outside diameter of 0.33mm) for the pen-injector to penetrate the center of the disc vertically in a manner consistent with its intended use. The penetration should be performed for at least the maximum number of intended use. Use a new needle for each puncture. After each puncture, purge the lumen of the needle with water, pass the water through the quick filter paper. After all the piercing, empty the cartridge content onto the filter paper. Make sure no fragments are left in the barrel. Count the number of fragments on the filter paper (equivalent to a particle size over 50μm) with naked eyes. If necessary, confirm the number and size of fragments via a microscope, which shall comply with the enterprise specification or quality agreements.

3.2 Gliding performance

Put the plunger stopper into the barrel and fix it onto the material testing machine. Push the plunger stopper at the specified speed (such as 50mm/min±5mm/min), record the maximum force in gliding, which shall comply with the enterprise specification or quality agreements.

NOTE: Precapped cartridge systems for pen-injectors shall have their caps removed prior to testing.

3.3 Specific requirements for sterile components

3.3.1 Particulate matter

It is applicable to sterile-supplied components. 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.

3.3.2 Residual amount of ethylene oxide

It is used to evaluate the residual amount of sterilant in components 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. Take samples and test according to Determination of Ethylene Oxide for Pharmaceutical Packaging Materials and Containers (General Chapter 4209). The residual amount of ethylene oxide in each sample shall be less than 5μg.

3.3.3 Bacterial endotoxin

It is applicable to sterile supplied components. Seal the barrel with plunger stopper/disc that are free of bacterial endotoxin or specified in the enterprise specification or quality agreements, and prepare test solution according to Guideline for Bacterial Endotoxin Test (Guideline 9251). Then test according to Test for Bacterial Endotoxin (General Chapter 1143), and the result shall comply with the enterprise specification or quality agreements.

3.3.4 Sterility

It is applicable to sterile-supplied components. Sterility test can be carried out

159 referring to Guideline for Microbiological Test of Pharmaceutical Packaging Materials
160 and Containers (Guidelines 9653), and shall be sterile.

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