5201 General Chapter of Rubber Closures for Packages for Injections

1 Scope

This general chapter specifies the baseline requirements shall be complied with during the manufacturing and application of rubber closures for packages for injections.

This general chapter is applicable to the rubber closures used as part of injection packaging systems.

2 Classification

In addition to the classification in terms of base material, overall structure and pre-use treatment following General Chapter of Rubber Closures for Pharmaceutical Packages (General Chapter 5200), rubber closures for packages for injections could also be classified according to their intended uses and shapes, degree of contact with preparations, and the manner of clinical use.

2.1 In terms of the intended uses and shapes, rubber closures for packages for injections may be classified into rubber stoppers for glass bottles for infusions and glass vials for injections, rubber closures for plastic packaging systems and components for infusions, rubber closures for prefilled syringes and for pen-injectors, etc. Rubber closures for plastic packaging systems and components for infusions may be classified into cap liners for combination caps of plastic packaging systems, rubber stoppers and liners for administration ports of plastic infusion bags, and rubber stoppers for plastic infusion bottles, etc. Rubber closures for prefilled syringes may be classified into plunger stoppers and caps, including needle shields and tip caps. Rubber closures for pen-injectors may be classified into plunger stoppers and septums, which are generally used in combination with aluminum caps.

2.2 According to the degree of being in contact with preparations, the rubber closures may be classified into rubber closures in persistent contact, in transient contact and in indirect contact with preparations in terms of the direct contact time, or classified into rubber closures for packages for aqueous injections and for sterile powders for injection (including freeze-dried preparations for injection) in terms of the contact state.

2.3 In terms of the manner of clinical use, the rubber closures may be classified into rubber closures to be pierced and not to be pierced. Rubber closures to be pierced may be further classified into rubber closures singly pierced by infusion sets for intravenous administration (hereinafter referred to as rubber closures pierced by infusion sets), and singly or multiply pierced by hypodermic needles for product dissolution or transfer (hereinafter referred to as rubber closures singly or multiply pierced by hypodermic needles).

3 Overall Requirements

Rubber closures for packages for injections shall comply with the following requirements during the periods of manufacturing and use.

Rubber closures for packages for injections shall comply with the relevant provisions specified in Overall Requirements of General Chapter of Rubber Closures for Pharmaceutical Packages (General Chapter 5200). For wash-free and ready-to-use rubber closures for packages for injections, validation of the processes of depyrogenation and sterilization (when applicable) shall be conducted.

For the rubber closures for freeze-dried preparations, attention should be paid to the structure design, such as the position and size of the positioning element, which should not adversely affect the sealing performance of the rubber closures. Attention should be paid to residual moisture of the rubber closures, on which the possible effects of the formulations and processes should be evaluated when necessary. Appropriate techniques could be used to assess the water content and the effectiveness of the drying process conditions, and water content of rubber closures shall be effectively controlled before use following the stability requirements of the pharmaceutical products.

For the design of rubber closures for prefilled syringes and for pen-injectors, the different functional requirements of manual or automatic use should be taken into account.

4 Quality Control

For rubber closures for packages for injections, the relevant tests specified in Quality Control of General Chapter of Rubber Closures for Pharmaceutical Packages (General Chapter 5200) and the following tests shall be performed

4.1 Physicochemical Tests

4.1.1 Water content. Applied to ready-to-use rubber closures for packages for freeze-dried preparations for injection. When necessary, perform the test according to Method II of Determination of Water for Rubber Closures (General Chapter 4221), and the results shall comply with the relevant specifications of enterprise standards or quality agreements.

4.1.2 Silicone oil on the surface. Applied to rubber closures for packages for injections which are in direct contact with pharmaceutical products when whose quality could be affected by the silicone oil. When necessary, perform the test according to Determination of Silicone Oil on the Surface of Rubber Closures (General Chapter 4222), and the results shall comply with the relevant specifications of enterprise standards or quality agreements.

4.2 Clinical Use Performance Tests

Including but not limited to the tests specified in this general chapter, corresponding tests shall be carried out according to the production processes and clinical use of the pharmaceutical products. If rubber closures would be penetrated by hypodermic needles and infusion sets simultaneously when in clinical use, corresponding tests of rubber closures pierced by infusion sets and pierced by hypodermic needles are carried out respectively when necessary, and all results shall comply with the relevant requirements.

4.2.1 Rubber Stoppers for Glass Bottles for Infusion and Glass Vials for Injections

The following tests are carried out for rubber stoppers for glass bottles for infusion and glass vials for injections. For rubber stoppers for packages for freeze-dried preparations, the following tests are carried out after the samples were pretreated under freezing conditions specified in enterprise standards or quality agreements.

4.2.1.1 Fragmentation. Applied to the rubber stoppers pierced by infusion sets. Perform the test according to Method I of Test for Fragmentation of Closures and Seals for Parenteral Preparations (General Chapter 4016). The number of observed particles is not more than 20.

Applied to the rubber stoppers pierced by hypodermic needles. Perform the test according to Method II of Test for Fragmentation of Closures and Seals for Parenteral Preparations (General Chapter 4016). The number of observed particles is not more than 5.

4.2.1.2 Penetration force. Applied to the rubber stoppers pierced by infusion sets. Perform the test according to Method I of Test for Penetrability of Closures and Seals for Parenteral Preparations (General Chapter 4015). The average of all test samples is not more than 75 N and all test samples does not exceed 80 N, and no rubber stopper is pushed into the bottle during the piercing.

Applied to the rubber stoppers pierced by hypodermic needles. Perform the test according to Method II of Test for Penetrability of Closures and Seals for Parenteral Preparations (General Chapter 4015), and the penetration force for all test samples does not exceed 10 N.

4.2.1.3Spike retention and sealability Capacity. Applied to the rubber stoppers pierced by infusion sets. Take 10 samples pretreated according to Method I of Test for Penetrability of Closures and Seals for Parenteral Preparations (General Chapter 4015), and 10 matched bottles for injections filled to the nominal volume with water, then crimp the matched aluminum caps or aluminum-plastic caps. Use the metal spikes described in Method I of Test for Penetrability of Closures and Seals for Parenteral Preparations (General Chapter 4015) to vertically pierce the marked area until complete penetration is achieved. Position the bottles with the bottom end up and attach a mass of 0.5 kg to each spike. Spikes shall be retained in the closures for 4h and no liquid leakage shall be observed at the puncture sites of the stoppers.

4.2.1.4 Self-sealing Capacity. Applied to rubber stoppers multiply pierced by hypodermic needles, and need to be performed only after being fitted with other assembly components. Take 10 samples pretreated according to Method II of Test for Penetrability of Closures and Seals for Parenteral Preparations (General Chapter 4015).Take 10 matched vials for injections filled to the nominal volume with water, then fit the above rubber stoppers and secure with the matched fasteners. Use injection needles defined in Method II of Test for Penetrability of Closures and Seals for

Parenteral Preparations (General Chapter 4015)to vertically pierce the different puncture sites of each stopper3 times, changing a new needle after every 10 punctures. Immerse the above test samples bottom end up in 0.1% methylene blue solution in a container with a vacuum pump, reduce the pressure by 27kPa and hold for 30 min, then restore to atmospheric pressure and hold for another30 min. Take the test samples out, rinse the outsides of the vials with water. Any trace of methylene blue solution is observed in none of the containers. For rubber stoppers specified the test of self-sealing capacity, the test of Sealability of Closures for Containers is generally not required further.

4.2.1.5 Sealability of closures for containers. Applied to the rubber stoppers singly pierced by hypodermic needles, and need to be performed only after being fitted with other assembly components. Take 10 samples pretreated according to Method II of Test for Penetrability of Closures and Seals for Parenteral Preparations (General Chapter 4015). Take 10 matched vials for injections filled to the nominal volume with water, then fit the above rubber stoppers and secure with the matched fasteners. Immerse the above test samples bottom end up in 0.1% methylene blue solution in a container with a vacuum pump, reduce the pressure by 27kPa and hold for 30 min, then restore to atmospheric pressure and hold for another 30 min. Take the test samples out, rinse the outsides of the vials with water. Any trace of methylene blue solution is observed in none of the vials. If direct observation is impossible, the solution may be taken out by a suitable method and inspected visually. The solution does not appear blue.

4.2.2 Rubber Closures for Plastic Packaging Systems and Components for Infusions

The following tests are carried out for cap liners for combination caps of plastic packaging systems. For other rubber closures for plastic packaging systems and components for infusions, taking account of the characteristics of packaging systems and the manners of clinical use, the relevant clinical use performance tests specified in enterprise standards or quality agreements shall be complied with.

4.2.2.1 Fragmentation. Perform the test according to Method III of Test for Fragmentation of Closures and Seals for Parenteral Preparations (General Chapter 4016)

(The plastic packaging systems for infusions may act as the supporting device. Fit the cap liners to matched plastic infusion containers separately, fill the containers to the nominal volume with water, seal and sterilize according to the pretreatment conditions.). The number of observed particles shall be not more than 20.

4.2.2.2 Penetration force. Perform the test according to Method III of Test for Penetrability of Closures and Seals for Parenteral Preparations (General Chapter 4015) (The plastic packaging systems for infusions may act as the supporting device. Fit the cap liners to matched plastic infusion containers separately, fill the containers to the nominal volume with water, seal and sterilize according to the pretreatment conditions.). The average of all test samples are not more than 75 N and all test samples do not exceed 80 N.

4.2.2.3 Spike retention and sealability. Need to be performed only after the rubber closures are fitted with other assembly components. Fit 10 cap liners to matched plastic infusion containers separately, fill the containers to the nominal volume with water and seal. Use the plastic spike described in Method III of Test for Penetrability of Closures and Seals for Parenteral Preparations (General Chapter 4015) to vertically pierce the marked area until complete penetration is achieved. Position the containers with the bottom end up and attach a mass of 0.3 kg to each spike. Spikes shall be retained in the closures for 4h and no liquid leakage shall be observed at the puncture sites of the closures.

4.2.3 Rubber Closures for Prefilled Syringes

Only after rubber closures for prefilled syringes are subassembled or assembled with other assembly components，corresponding tests need to be performed, and the results shall comply with the relevant specifications of the General Chapter of Prefilled Syringes(General Chapter 5510).

4.2.4 Rubber Closures for Pen-Injectors

Only after rubber closures for pen-injectors are subassembled or assembled with other assembly components，corresponding tests need to be performed, and the results shall comply with the relevant specifications of the General Chapter of Cartridge Systems for Pen-Injectors(General Chapter 5520).

4.3 Other Tests

4.3.1 Particulate matter. Applied to wash-free and ready-to-use rubber closures, and tested when necessary. Perform the test according to Determination of Particulate Matter for Pharmaceutical Packaging Materials and Containers (General Chapter 4206), and the results shall comply with the specifications in the following table.

packaging System/Assembly	Rubber Closures	Limit (particles/mL)	
		10 μm and above	25 μm and above
Packaging System for Injections	Stopper	30	3
Packaging System for Sterile Powders for Injections	Stopper	60	6

4.3.2 Bioburden. When necessary, perform the test of bioburden according to Guideline on Microbiological Testing of Pharmaceutical Packaging Materials (Guideline 9653), and the results shall comply with the relevant specifications of enterprise standards or quality agreements. For rubber stoppers for packages for injections specified the test of sterility, the test of Bioburden is generally not required further.

4.3.3 Sterility. Applied to ready-to-use rubber closures. When necessary, perform the test of sterility according to Guideline on Microbiological Testing of Pharmaceutical Packaging Materials (Guideline 9653), and the results shall comply with the specifications.

4.3.4 Bacterial endotoxins or pyrogens. Applied to wash-free and ready-to-use rubber closures. When necessary, perform the test of bacterial endotoxins according to Guidelines for the Application of Bacterial Endotoxin Test (Guideline 9251), and the results shall comply with the relevant specifications directed in the specific monograph of pharmaceutical products. If the pharmaceutical product and its relevant specifications cannot be defined, the results of bacterial endotoxin shall be less than 0.25 EU/mL, or take an appropriate amount of the test solution to perform the test of pyrogens according to Test for Pyrogens (General Chapter1142), and the results shall comply with the specifications.

5 Packaging and Storage

The packaging materials in direct contact with rubber closures shall comply with

the relevant requirements of pharmaceutical packages. The packages for ready-to-use rubber closures should be resistance to the sterilization processes applied, and cause no adverse influence on the effects of sterilization. The sealed packages shall be of enough integrity, and the primary and secondary packaging as a whole should meet the requirements for protection performance during the transportation and storage. The packages for ready-to-use rubber closures should meet the requirements of quality management and convenience of pharmaceutical production.

The rubber closures should be stored in the dry, clean and well-ventilated indoor environment.

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