**5200 General Chapter of Rubber Closures for Pharmaceutical Packages**

**1 Scope**

This general chapter specifies the baseline requirements for the manufacturing, application and quality control of rubber closures for pharmaceutical packages (hereinafter referred to as rubber closures).

This general chapter is applicable to the rubber closures used as part of a pharmaceutical product packaging system.

**2 Terms and Definitions**

The following terms and definitions apply to the relevant general chapters of rubber closures.

2.1 Rubber

Elastic high-molecular polymer materials with reversible deformation which can be substantially deformed under stress but recovers quickly to near its original shape when the stress is removed, and may be swelled but practically insoluble in hot organic solvents after being crosslinked (such as vulcanization process). including natural rubber which is made from gum extracted from botanical sources, such as *Hevea brasiliensis*, and synthetic rubber which is produced by polymerization of various monomers.

2.2 Rubber Closure

Elastomeric components with different structures and shapes, obtained by crosslinking (vulcanization) of one or various kinds of rubber as base polymer, using necessary additives, such as fillers, curatives, etc., to act as closures when combined with other components of container-closure systems.

**3 Classification**

Rubber closures may be classified in terms of intended use, base material, overall structure, pretreatment, etc..

3.1In terms of intended use, rubber closures may be classified into rubber closures for packages for injections, inhalation preparations, oral preparations, or other preparations.

3.2In terms of base material, rubber closures may be classified into rubber closures made of (halogenated) butyl rubber, polyisoprene rubber, silicone rubber, ethylene-propylene rubber, other synthetic rubber, etc., and base material by mixing or lamination of different rubbers.

3.3In terms of overall structure, rubber closures may be classified into rubber closures with ordinary, multilayer or filmed structure. According to the film-forming process, filmed rubber closures may be further divided into rubber closures with laminated, coated or deposited film. Common film materials include organic fluorine, silicone and other plastic materials.

3.4In terms of pretreatment, rubber closures may be classified into routine, wash-free, wash-free and sterilization-free rubber closures which are also referred to as ready-to-use rubber closures.

**4 Overall requirements**

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

**4.1 Manufacturing Requirements**

During the formulation design, research and development of rubber closures, the regulatory compliance and safety of relevant materials and their compositions shall be confirmed. Raw materials and processing aids that significantly affect the quality of pharmaceutical products would be avoided, the identification and control of toxic or harmful impurities shall be strengthened, and attention should be paid to organic small molecule residues, metal residues or other relevant extractables of rubber closures.

The formulation and manufacturing processes of rubber closures shall be fully validated and effectively controlled in accordance with relevant good manufacturing practices to ensure the quality homogeneity. If barrier materials are used in filmed rubber closures, the quality control of film integrity and thickness should be strengthened.

Rubber closures shall be appropriately cleaned and dried. Selected water for gross rinse and precisely washing shall be of appropriate quality to comply with the requirements for their intended use, and validation of the effectiveness of the cleaning procedures shall be carried out when necessary. If siliconization is performed, dimethicone that meets the requirements for pharmaceutical use should be used, and the control of the amount of silicone oil and the uniformity of siliconization should be strengthened. If sterilization procedures are required, the effectiveness of sterilization shall be validated and its impact on the performance of rubber closures should be fully assessed.

During the processes of manufacturing, packaging, storage and transportation of rubber closures, attention should be paid to the relevant requirements of the quality management of the pharmaceutical products to be packaged. Cleaning, sterilization (when applicable) and packaging procedures of wash-free or ready-to-use rubber closures shall be performed in a controlled environment, taking the cleanliness requirements of pharmaceutical products to be packaged into account. Attention should be paid to the protectability of packages and shelf life of wash-free and ready-to-use rubber closures.

**4.2 Application Requirements**

Before rubber closures being used, relevant evaluations and tests of Guideline on Biological Evaluation and Test Selection of Pharmaceutical Packaging Materials (Guideline 9651) shall be carried out. The requirements of compatibility studies should be met when applicable. Risk assessments of compounds of concern and elemental impurities should be focused on, and the performance of processing compatibility in the procedures of packaging pharmaceutical products, the protection ability covering the entire life cycle of the pharmaceutical products, the functionality in the clinical application of pharmaceutical products should be assessed and confirmed.

Attention should be paid to the suitability of shape and dimensions of rubber closures with other components. For filmed rubber closures, the coverage area of the film and the performance of the sealing surface should be concerned to avoid possible adverse effects on the sealability due to partial shedding of the film or the difference in properties of various materials.

The critical quality attributes of rubber closures shall be defined based on the relevant necessary studies and assessments according to the requirements of risk management throughout the life cycle of pharmaceutical products, and strictly controlled in accordance with enterprise standards or quality agreements to protect the safety, efficacy and quality controllability of the pharmaceutical products.

**5 Quality Control**

The following identification and physicochemical tests shall be carried out for rubber closures，as well as clinical use performance tests and other tests set forth in general chapters of each category. Including but not limited to the relevant provisions of this general chapter and general chapters of each category, relevant parties shall reasonably define the tests, methods, limits and testing rules to carry out quality control of rubber closures for specific application.

**5.1 Identification**

Applied to identify the base materials and film materials (if any) of rubber closures. To improve the reliability of the characterization of rubber closures, it is advisable to use various identification methods including the following procedures.

5.1.1 Infrared Spectroscopy. Applied to the base materials of rubber closures. Cut the sample, and examine the cut surface according to Infrared Spectroscopy of Pharmaceutical Packaging Materials (General Chapter 4002, Method II).If rubber materials (with much carbon black) cannot reflect the infrared light, perform the test according to the Infrared Spectroscopy of Pharmaceutical Packaging Materials (General Chapter 4002, Method I-3). The infrared spectrum of the base material (including each layer of material) shall comply with the relevant specifications of enterprise standards or quality agreements.

Applied to the film materials of filmed rubber closures. Wipe the film with acetone or other suitable solvents, evaporate to dryness, and examine the wiped part according to Infrared Spectroscopy of Pharmaceutical Packaging Materials (General Chapter 4002, Method II). The infrared spectrum of the film shall comply with the relevant specifications of enterprise standards or quality agreements.

5.1.2 Ash. Applied to the rubber closures containing inorganic fillers. Test according to Determination of Ash in Rubber Closures (General Chapter 4220). If above 10%, the percentage content of ash should not exceed ±2.0% of that defined in enterprise standards or quality agreements, and the ash content of 10% or less shall comply with the relevant specifications of enterprise standards or quality agreements.

5.1.3 Density. Applied to silicone rubber closures. Heat 2 g of the samples under reflux with 100 mL of water for 2 hours, dry at 80°C, and then test according to Determination of Density of Pharmaceutical Packaging Materials (General Chapter 4012). The result shall be 1.05 to 1.25 g/cm3.

**5.2 Physicochemical Tests**

Applied to routine assessment of possible leachables from rubber closures. Tests are usually performed for water-soluble substances and specific residues under controlled extraction conditions to reduce the relevant risks of rubber closures when used actually. If rubber closures are used for preparations containing non-aqueous solvents, the possible effects should be evaluated, and if necessary, to be controlled by enterprise standard or quality agreements.

**5.2.1 Water-soluble Substances**

For the rubber closures subjected to steam sterilization, perform the following corresponding tests according to Determination of Extractables for Pharmaceutical Packaging Materials and Containers (General Chapter 4204). If other sterilization procedures are used, such as ethylene oxide sterilization, radiation sterilization, etc., the possible effects of these procedures should be assessed, and if necessary, be controlled by enterprise standard and quality agreements.

The following procedures are applied to the (halogenated) butyl rubber and polyisoprene rubber closures. Take an appropriate amount of uncut samples (with a total surface area close to 200 cm2) and prepare the test solution (boiling and rinsing procedures are exempted for wash-free and ready-to-use rubber closures) and blank solution according to Method II in Table 1 of Determination of Extractables for Pharmaceutical Packaging Materials and Containers (General Chapter 4204).

The following procedures are applied to the silicone rubber closures. Take an appropriate amount of uncut samples (mass close to 25 g) and prepare the test solution and blank solution according to Method XI in Table 1 of Determination of Extractables for Pharmaceutical Packaging Materials and Containers (General Chapter 4204).

5.2.1.1 Clarity and Color. The test solution shall be clear and colorless, otherwise not more opalescent than Reference suspension 2 or not more intensely colored than yellowish green No.5 color standard.

5.2.1.2 Change of pH. The rubber closures for packages for injections or for oral preparations shall comply with the specifications in Table 1 or Table 2, respectively. If the requirements are met, the test of Acidity or Alkalinity could be exempted, otherwise shall be carried out, and whose results are taken to make the judgment.

5.2.1.3 Acidity or Alkalinity. Not more than 0.3 mL of sodium hydroxide volumetric solution (0.01mol/L) is consumed, or not more than 0.8 mL of hydrochloric acid (0.01mol/L) is consumed.

5.2.1.4 Absorbance. For the maximum absorbance of the test solution at wavelengths between 220 and 360 nm, the rubber closures for packages for injections or for oral preparations shall comply with the specifications in Table 1 or Table 2, respectively.

5.2.1.5 Reducing substances. The rubber closures for packages for injections or for oral preparations shall comply with the specifications in Table 1 or Table 2, respectively.

5.2.1.6 Residue on evaporation. The rubber closures for packages for injections or for oral preparations shall comply with the specifications in Table 1 or Table 2, respectively.

5.2.1.7 Conductivity. The rubber closures for packages for injections shall comply with the specifications in Table 1.

Table 1

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Packaging System/Assembly | Rubber Closures | Limits | | | | |
| Change of pH | Absorbance | Reducing substances (ml) | Residue on evaporation (mg) | Conductivity (μS/cm) |
| Packaging System for Injections | Stopper | 1.0 | 0.1 | 3.0 | 2.0 | 10.0 |
| Packaging System for Sterile Powders for Injection | Stopper | 2.0 | 0.2 | 7.0 | 4.0 | 20.0 |
| Prefilled Syringes and Pen-injectors | Plunger | 1.0 | 0.1 | 3.0 | 2.0 | 20.0 |
| Tip cap | 2.0 | 0.2 | 3.0 | 2.0 | 20.0 |
| Needle shield | 3.0 | 0.3 | 7.0 | 4.0 | 40.0 |
| (Multilayer) Septum | 2.0 | 0.2 | 3.0 | 2.0 | 20.0 |
| Combination Caps of Plastic Infusion Containers | Cap Liner | 3.0 | 0.3 | 3.0 | 4.0 | 40.0 |

Table 2

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Packaging System | Rubber Closures | Limits | | | |
| Change  of pH | Absorbance | Reducing substances (ml) | Residue on evaporation (mg) |
| Packaging System for Oral Preparations | Silicone rubber closures | 1.0 | 0.1 | 1.0 | 2.0 |
| (Halogenated) butyl rubber, polyisoprene rubber closures | 3.0 | 0.3 | 7.0 | 4.0 |

5.2.1.8 Ammonia. Applied to rubber closures using or generating compounds containing amine groups. Not more than 0.0002%.

5.2.1.9 Metal Ions. When applicable, taking into account of the possible hazardous elements and formulation elements in the rubber closures, perform the test according to the Determination of Element Impurities in Drug Packaging Materials (General Chapter 4214). The results shall comply with the relevant specifications of enterprise standards or quality agreements.

5**.2.2 Specific Residue**

The type and the content of the residues mainly depend on the formulation and process of rubber closures. The following test of Volatile sulfides shall be carried out for (halogenated) butyl rubber and polyisoprene rubber closures, the following tests of Phenylated compounds, Substances soluble in hexane, Volatile matter, Mineral oils and Residual peroxides should be carried out for silicon rubber closures according to the Determination of Specific Residues in Silicon Rubber Closures (General Chapter 4223).

5.2.2.1 Volatile sulfides. Applied to rubber closures using sulfur or sulfur-containing compounds. Test according to Determination of Volatile Sulfides in Rubber Closures (General Chapter 4219). Any black stain caused by test samples is not more intense than that of the reference (not more than 1.0μg/cm2, calculated as sulfur).

5.2.2.2 Phenylated compounds. The maximum absorbance is not greater than 0.4.

5.2.2.3 Substances soluble in hexane. The residue weighs not more than 15 mg.

5.2.2.4 Volatile matter. Maximum 2.0 per cent.

5.2.2.5 Mineral oils. Fluorescence shall not appear, and if appears, it is not greater than that of the reference solution.

5.2.2.6 Residual peroxides. Applied to silicone rubber closures prepared using peroxides. The difference between the titration volumes of test sample and the blank is not greater than 2.0 mL (equals to 0.08 per cent, calculated as dichlorobenzoyl peroxide).

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