Guideline for Packaging System of Preparations for Inhalation

This Guideline outlines the general requirements for the production, use, and quality control of packaging system and components for preparations for inhalation. Enterprises should conduct risk assessment and prevention/control based on the idea of risk management, combined with the requirements of preparations for inhalation, and the characteristics and uses of packaging system and components. The administrative management of packaging system and components for preparations for inhalation should be implemented in accordance with relevant regulations of their categories.

Packaging system for preparations for inhalation refers to the packaging systems that accommodate, protect, and deliver preparations for inhalation, consisting of packaging components that come into direct contact with the medicinal product, as well as components that do not come into direct contact with the medicinal product but have additional protective and functional properties for the medicinal product. Packaging components for preparations for inhalation refer to one or a group of components in the packaging system for preparations for inhalation, including drug packaging container, dosing device, protective secondary packaging materials, etc.

According to the category of preparation, common packaging systems for preparations for inhalation include packaging system for metered dose inhalers (MDI), packaging system for dry powder inhalers (DPI), packaging system for liquid preparations for inhalation and packaging system for inhalation sprays.

The packaging system for MDIs typically includes a metering valve, a pressure container, a dosing device (e.g., actuator), protective secondary packaging materials (e.g., aluminum foil pouches), etc. Pressurized containers are usually metal cans, such as aluminum alloy cans and stainless steel cans. Aluminum alloy cans are classified into different types based on surface treatment, such as uncoated, coated, anodized, and plasma-treated.

There are various types of DPIs, and the packaging system for DPIs referred in this Guideline is mainly applicable to the device types of formulation supplied in single dose capsules, multiple dose unit blisters, and multiple dose reservoir. The packaging system for capsule-type DPIs consists of capsules in direct contact with the medicinal product, protective secondary packaging materials (e.g., pharmaceutical composite sheets and aluminum foil pouches), and a dosing device for drug delivery during use. The packaging system for blister-type DPIs contains an aluminum-plastic blister in direct contact with the medicinal product and a dosing device composed of multiple components. The aluminum-plastic blister is embedded in the dosing device, and if necessary, protective secondary packaging materials (e.g., aluminum foil pouches) are used to package the whole dosing device. The packaging system for reservoir-type DPIs generally contains a powder reservoir in direct contact with the medicinal product and a dosing device composed of multiple components. The powder reservoir is embedded in the dosing device, and if necessary, protective secondary packaging materials (e.g., aluminum foil pouches) are used to package the whole dosing device.

The packaging system for liquid preparations for inhalation mainly includes plastic ampules and protective secondary packaging, glass injection vials and seals (e.g., aluminum-plastic combination caps and stoppers), and glass ampules.

The packaging system for inhalation sprays generally contains a packaging container in direct contact with the medicinal product and a dosing device composed of multiple components. When in use, the packaging container is embedded into the dosing device.

I. Production Requirements

The production and assembly of the packaging system and components for preparations for

inhalation should comply with relevant good manufacture practice and the provisions of the General Chapter for preparations for inhalation (General Chapter 0111) to ensure compliance with pharmaceutical requirements. The component materials used include plastic, rubber, metal, glass, and other categories, and should comply with the production requirements of the relevant material general Chapters. The component materials that come into direct contact with the medicinal product should not affect the quality and safety of the medicinal product, and attention should be paid to the research and control of extractables.

It should be ensured that the components that require precision machining in the packaging system for preparations for inhalation are precise in terms of shape and size, and have and maintain appropriate structural strength (e.g., meeting the requirements of deformation pressure, etc.). Attention should be paid to the movement and compatibility status among components so as to ensure the sealing and functionality of the packaging system during the validity and use period.

Liquid preparations for inhalation and inhalation sprays are sterile preparations, and relevant requirements of Good Manufacturing Practice should be referred to for the production and packaging processes of components in direct contact with the medicinal product (e.g., plastic ampules).

II. Application Requirements

The components used should comply with the application requirements specified in the general chapters on relevant materials.

When necessary, referring to the Guidelines on Biological Evaluation and Test Selection for Pharmaceutical Packaging Materials (Guideline 9629)，key component materials and/or packaging system should be evaluated and tested.

Components that come into direct contact with the medicinal product should meet the compatibility requirements for drug product, and attention should be paid to risk assessment of leachables and research on adsorption of drug. For semi-permeable packaging system, a risk assessment should also be conducted on the leachables from adhesive and ink in the label.

When necessary, based on the risk level of medicinal product, referring to the Research Guidelines on Sealing Properties of Pharmaceutical Packaging Systems (Guideline 9628)，an appropriate method for evaluation should be selected to ensure compliance with the requirements for integrity of pharmaceutical packaging system. For semi-permeable packaging system, their air permeability and water permeability, as well as their impact on quality of the medicinal product, should be investigated.

Research and control should be conducted on the protection and functionality of packaging system and components in accordance with the requirements of the General Chapter for Preparations for Inhalation (General Chapter 0111). The packaging system or device with drug delivery function should meet quality requirements such as total number of actuations/puffs/sprays delivered and dose content uniformity during its valid and use period. Attention should be paid to the study of the impact of dropping test on the performance of the dosing device. For barrier packaging with additional functions (e.g., protective secondary packaging aluminum foil pouches), bottle caps (such as bacterial-resistant caps, tamper-evident caps), etc., their additional functions and impact on the quality of the medicinal product need to be investigated, and attention should be paid to the stability of the drug product within valid period after opening.

For the packaging system for DPIs, attention should be paid to the influence of airflow resistance. For the capsules used for capsule-type DPIs, attention should be paid to their protective and functional indicators, including but not limited to hygroscopicity, emptying performance, puncture performance, fragility, etc. For the aluminum-plastic blisters used for blister-type DPIs, attention should be paid to its emptying performance, welding strength, sealing performance, etc.

III. Quality Control

1. Physical performance

For the packaging system for MDIs, the tests should include but not limited to the appearance, size, weight difference, identification (such as material identification of key components of the metering valve, identification of coating/treatment film layer of the pressurized container), integrity of coating/treatment film layer of the pressurized container, and the shape, size, and key nozzle parameters of the actuator, etc.

For the packaging system for DPIs, appropriate quality controls should be selected based on the dosing device and drug type, such as component appearance, shape, size, weight difference, identification (e.g., material identification of key components in direct contact with the medicinal product), and compatibility performance, etc.

For the packaging system for liquid preparations for inhalation, if semi-permeable plastic ampules are used, attention should be paid to the impact of their air permeability and water permeability on the medicinal product, and corresponding quality control tests should be selected.

For the packaging system for inhalation sprays, the tests should include but not limited to appearance, shape, size, identification (e.g., material identification of key components in direct contact with the medicinal product), and compatibility performance, etc.,

2. Chemical performance

For components that come into direct contact with the medicinal product, attention should be paid to the safety risks of leachables to the medicinal product. If necessary, appropriate tests and specifications for leachables can be developed according to the Determination of Leachables in Pharmaceutical Packaging Materials (General Chapter 4204). With reference to the ICH Q3D Guideline for Elemental Impurities, the sources of known or potential elemental impurities should be identified based on different materials and the manufacturing process, a risk assessment should be performed based on drug quality requirements, and conduct inspections，if necessary，according to the Determination of Elemental Impurities in Pharmaceutical Packaging Materials (General Chapter 4214).

3. Application performance

For the packaging system for MDIs, pressure resistance testing is required for the pressurized container to observe for any deformation, leakage, or rupture. The performance quality of packaging system should be tested to evaluate the compatibility of the metered valve, pressurized container, and actuator, as well as the delivery functionality of the metered valve.

For the packaging system for DPIs, the dosing device should undergo quality control testing in terms of airflow resistance, dust cover opening and closing resistance, and actuation or usage resistance within the valid period. For capsule-type DPIs, quality parameters such as the emptying performance, puncture performance, and fragility of the capsules should also be controlled. For blister-type DPIs, the quality parameters of the aluminum-plastic blister, such as emptying performance, welding strength, and sealing performance, should also be controlled.

For MDIs and inhalation sprays, it is necessary to investigate the uniformity of shot weight of the metering valve and the total number of actuations of the valve.

For the packaging system for liquid preparations for inhalation and inhalation sprays, the risk of particulate matter to the product should be considered, and if necessary, control requirements can be set according to the Determination of Particulate Matter in Pharmaceutical Packaging Materials (General Chapter 4206).

4. Microbial control

Referring to the Guideline for Microbiological Testing of Pharmaceutical Packaging Materials (Guideline 9627) ， the microbial limit, bioburden, or sterility of packaging system or components can be controlled, so as to ensure that the packaging system meets the requirements for preparations for inhalation.

IV. Packaging and Storage

The packaging of components of the packaging system for preparations for inhalation should comply with pharmaceutical requirements, and the components should be stored in a dry and clean place.

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