Chapter 0111 – Inhalation products

**General requirements**

- Any antibacterial agents should comply with the antibacterial potency test. Liquid inhalation products should be sterile.
- Any additives to powder formulations should be non-irritating to the respiratory tract. All device components should be non-toxic and not react with the drug substance.
- An adequate fine particle dose should deposit in the lungs which should be suitably characterised. The drug substance particle size should be controlled at 10μm or less and most should be 5μm or less.
- For multi dose inhalers, delivered dose uniformity must be assessed both within an individual inhaler (vitra) and between different inhalers (inter).
- Leak tests are required for inhalation aerosol products.
- Thepackage insert for metered dose aerosols shall state: (1) number of actuations per inhaler (2) amount of drug substance(s) delivered per actuation (3) number of actuations required to provide the minimum recommended dose (4) range of antibacterial agent if present.
- The package insert for capsule and blister inhalation products shall state (1) amount of drug substance per capsule or individual blister (2) that the capsule should be placed in the inhalation device for inhalation – it should not be swallowed (3) product shelf life (4) product storage conditions.

**Definition**

**Inhalation Aerosol (pMDI)**
Drug containing solution, suspension or emulsion, packaged and sealed together with appropriate propellants in a pressurised container fitted with a fixed volume metering valve system. Co-solvents, solubilizing agents and stabilisers may also be present.

**Dry Powder Inhalers (DPIs)**
Defined as solid microcrystalline drug substance alone or mixed with appropriate carriers and inhalated by patients into their lungs using a special powder inhaler. The powder is formulated as a capsule, blister or a multi-dose reservoir.

**Delivered Dose Uniformity**

- Use standard delivered dose testing equipment (Ph. Eur).
- Determine 10 delivered doses in total: initial 3 doses, middle 4 doses, final 3 doses.
- Determine 1 dose from each of 10 individual inhalers as specified in the product specification.

**Result assessment:**
Preparation complete if 9 out of 10 results lie between 75 and 125% of the average value and all lie between 65 and 135%.

If 2 or 3 values lie outside the 75 - 125% limits, repeat the test for 2 more inhalers. Not more than 3 of the 10 values lie outside the limits of 75 – 125% and no value 65 – 135%.

**Number of Inhalations**
Take 1 inhaler and perform successive actuations to waste. The interval between each actuation should not be less than 5 seconds. The total number of actuations should not be less than the labelled total actuations.

**Fine Particle Dose**
Performed according to the Determination of Aerodynamic Characteristics of the Fine Particles of Inhalation Products (General Chapter 0951) using the defined equipment and testing procedure for the specified inhalation aerosol product.

**Result assessment:**
Calculated FPD should meet product specification requirement, and should not be less than 10% of labelled delivered dose.

**Microbial Limits**

- Achieve aseptic technique during manufacturing.
- Perform the microbial test for non-sterile products.

**Result assessment:**
Results should comply with limits for microbial enumeration test. Microorganism and microbial limit test (General chapters 1105, 1106 and 1107).

**Aerodynamic Size Distribution Assessment**

**General chapter <0951>** describes the test used to determine the fine particle characteristics of the aerosol clouds generated by preparations for inhalation. Three apparatuses are listed in <0951>:

**Apparatus 1: Glass Impinger**
- Apparatus A
- Apparatus 1 (w/o pre-separator)

**Apparatus 2: Andersen Cascade Impactor**
- Apparatus D
- Apparatus 3 (w/o pre-separator)

**Apparatus 3: Next Generation Impactor**
- Apparatus E
- Apparatus 5 (w/o pre-separator)

For nebulizers, DPIs, and pMDIs same as apparatus A in Ph.Eur. (8.0)

For DPIs, similar to apparatus E in Ph.Eur. (8.0), except that <0951> does not specify the volume of air to be drawn during collection.

For nebulizers, <0951> requires NS3 be cooled at 5°C to at least 30 minutes prior to use. Test should be conducted at 15 L/min flow rate.

**Summary**

The inhalation product attributes subject to testing in the Chinese Pharmacopoeia are similar to those listed in the European Pharmacopoeia and United States Pharmacopoeia. The monographs describing the Chinese Pharmacopoeia tests for delivered dose uniformity (DDU) and aerodynamic particle size distribution provide content that is generally consistent with current scientific approaches. The detailed requirements for DDU are aligned with the European Pharmacopoeia and differ slightly from the United States Pharmacopoeia. The aerodynamic size distribution methods are generally similar to the other two compendia although the fine particle dose (FPD) requirements are more specific than those in the other two compendia. As products are developed for use in China it will be useful to keep in mind the regional differences.

**Test**

- **Chinese Pharmacopoeia**: Pharm. Euro. USP
- **DDU – Sampling Inhalers used**
  - 1(+) 3 9
  - 1(+) 3 9
  - 1(+) 3 9
- **Microbial Limits**
  - 9 or 10 are 75-125% Avg and all 65-135% Avg.
  - 9 or 10 are 80-120% target and all 65-135% Avg.
  - 9 or 10 are 80-120% target and all 75-125% target.
- **FDP – Acceptance criteria**
  - not less than 15% (MDI) or 10% (DPI) of labelled delivered dose

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<tr>
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