Preparations for inhalation

Premixes occur in granulated, powdered, semi-solid or liquid form. Used as powders or granules, they are free-flowing and homogeneous; any aggregates break apart during normal handling. Used in liquid form, they are homogeneous suspensions or solutions which may be obtained from thixotropic gels or structured liquids. The particle size and other properties are such as to ensure uniform distribution of the active substance(s) in the final feed. Unless otherwise justified and authorised, the instructions for use state that the concentration of a premix in granulated or powdered form is at least 0.5 per cent in the medicated feeding stuff.

PRODUCTION

Active substance. An active substance intended for incorporation into a medicated premix complies with the requirements of the relevant monograph of the European Pharmacopoeia, unless already otherwise justified and authorised for existing premixes.

TESTS

Loss on drying (2.2.32). Unless otherwise justified and authorised, for premixes occurring in granulated or powdered form, maximum 15.0 per cent, determined on 3.000 g by drying in an oven at 100-105 °C for 2 h.

LABELLING

The label states:
– the category of animal for which the premix is intended,
– the instructions for the preparation of the medicated feeding stuffs from the premix and the basic feed,
– where applicable, the time that must elapse between the cessation of feeding of the medicated feeding stuff and collection of the material intended for human consumption.

DEFINITION

Inhalanda

Preparations for inhalation are liquid or solid preparations intended for administration as vapours or aerosols to the lung in order to obtain a local or systemic effect. They contain one or more active substances which may be dissolved or dispersed in a suitable vehicle.

Preparations for inhalation may, depending on the type of preparation, contain propellants, co-solvents, diluents, antimicrobial preservatives, solubilising and stabilising agents, etc. These excipients do not adversely affect the functions of the mucosa of the respiratory tract or its cilia.

Preparations for inhalation are supplied in multidose or single-dose containers. When supplied in pressurised containers, they comply with the requirements of the monograph on Pressurised pharmaceutical preparations (0523).

Preparations intended to be administered as aerosols (dispersions of solid or liquid particles in a gas) are administered by one of the following devices:
– nebuliser,
– pressurised metered-dose inhaler,
– dry-powder inhaler.

PRODUCTION

During the development of a preparation for inhalation which contains an antimicrobial preservative, the effectiveness of the chosen preservative shall be demonstrated to the satisfaction of the competent authority. A suitable test method together with the criteria for judging the preservative properties of the formulation are described in the text on Efficacy of antimicrobial preservation (5.1.3).

The size of aerosol particles to be inhaled is controlled so that a significant fraction is deposited in the lung. The fine-particle characteristics of preparations for inhalation are determined by the method for Aerodynamic assessment of fine particles (2.9.18).

In assessing the uniformity of delivered dose of a multidose inhaler, it is not sufficient to test a single inhaler. Manufacturers must substitute procedures which take both inter- and intra-inhaler dose uniformity into account. A suitable procedure based on the intra-inhaler test would be to collect each of the specified doses at the beginning, middle and end of the number of doses stated on the label from separate inhalers. Pressurised metered-dose inhalers are tested for leakage. All inhalers are tested for extraneous particulate contamination.

LABELLING

For metered-dose preparations the label states:
– the delivered dose, except for preparations for which the dose has been established as a metered-dose or as a predispensed-dose,
– where applicable, the number of deliveries from the inhaler to provide the minimum recommended dose,
– the number of deliveries per inhaler.

The label states, where applicable, the name of any added antimicrobial preservative.

Liquid preparations for inhalation

Three categories of liquid preparations for inhalation may be distinguished:
A. preparations intended to be converted into vapour,
B. liquid preparations for nebulisation,
C. pressurised metered-dose preparations for inhalation.

Liquid preparations for inhalation are solutions or suspensions, dispersions. Dispersions are readily dispersible on shaking and they remain sufficiently stable to enable the correct dose to be delivered. Suitable excipients may be used.

A. PREPARATIONS INTENDED TO BE CONVERTED INTO VAPOUR

DEFINITION

Preparations intended to be converted into vapour are solutions, suspensions or solid preparations. They are usually added to hot water and the vapour generated is inhaled.

B. LIQUID PREPARATIONS FOR NEBULISATION

DEFINITION

Liquid preparations for inhalation intended to be converted into aerosols by continuously operating nebulisers or metered-dose nebulisers are solutions, suspensions or emulsions. Suitable co-solvents or solubilisers may be used to increase the solubility of the active substances. Liquid preparations for nebulisation in concentrated form for use in continuously operating nebulisers are diluted to the prescribed volume with the prescribed liquid before use. Liquids for nebulisation may also be prepared from powders.
The pH of the liquid preparations for use in continuously operating nebulisers is not lower than 3 and not higher than 8.5. Suspensions and emulsions are readily dispersible on shaking and remain sufficiently stable to enable the correct dose to be delivered. Aqueous preparations for nebulisation supplied in multidose containers may contain a suitable antimicrobial preservative at a suitable concentration except where the preparation itself has adequate antimicrobial properties. Continuously operating nebulisers are devices that convert liquids into aerosols by high-pressure gases, ultrasonic vibration or other methods. They allow the dose to be inhaled at an appropriate rate and particle size which ensures deposition of the preparation in the lungs. Metered-dose nebulisers are devices that convert liquids into aerosols by high-pressure gases, ultrasonic vibration or other methods. The volume of liquid to be nebulised is metered so that the aerosol dose can be inhaled with one breath.

C. PRESSURISED METERED-DOSE PREPARATIONS FOR INHALATION

DEFINITION
Pressurised metered-dose preparations for inhalation are solutions, suspensions or emulsions supplied in special containers equipped with a metering valve and which are held under pressure with suitable propellants or suitable mixtures of liquefied propellants, which can act also as solvents. Suitable cosolvents, solubilisers and stabilisers may be added. The delivered dose is the dose delivered from the inhaler to the patient. For some preparations, the dose has been established as a metered-dose. The metered-dose is determined by adding the amount deposited within the device to the delivered dose. It may also be determined directly.

TESTS

Uniformity of delivered dose. Containers usually operate in an inverted position. For containers that operate in an upright position, an equivalent test is applied using methods that ensure the complete collection of the delivered dose. In all cases, prepare the inhaler as directed in the instructions to the patient. The dose collection apparatus must be capable of quantitatively capturing the delivered dose. The following apparatus and procedure may be used. The apparatus (Figure 0671-1) consists of a filter-support base with an open-mesh filter-support, such as a stainless steel screen, a collection tube that is clamped or screwed to the filter-support base, and a mouthpiece adapter to ensure an airtight seal between the collection tube and the mouthpiece. Use a mouthpiece adapter which ensures that the front face of the inhaler mouthpiece is flush with the front face of the sample collection tube. The vacuum connector is connected to a system comprising a vacuum source and a flow regulator. The source should be adjusted to draw air through the complete assembly, including the filter and the inhaler to be tested, at 28.3 ± 1.5 litres/min. Air should be drawn continuously through the apparatus to avoid loss of the active substance into the atmosphere. The filter support base is designed to accommodate 25 mm diameter filter disks. The filter disk and other materials used in the construction of the apparatus must be compatible with the active substance and solvents that are used to extract the active substance from the filter. One end of the collection tube is designed to hold the filter disk tightly against the filter-support base. When assembled, the joints between the components of the apparatus are airtight so that when a vacuum is applied to the base of the filter, all of the air drawn through the collection tube passes through the inhaler. Unless otherwise prescribed in the instructions to the patient, shake the inhaler for 5 s and discharge one delivery to waste. Fire the inverted inhaler into the apparatus, depressing the valve for a sufficient time to ensure complete discharge. Repeat the procedure until the number of deliveries that constitute the minimum recommended dose have been sampled. Quantitatively collect the contents of the apparatus and determine the amount of active substance. Repeat the procedure for a further 2 doses. Discharge the device to waste, waiting not less than 5 s between actuations until \( n/(2+r+1) \) deliveries remain, where \( n \) is the number of deliveries stated on the label. Collect 4 doses using the procedure described above. Discharge the device to waste, waiting not less than 5 s between actuations until 3 doses remain. Collect these 3 doses using the procedure described above. For preparations containing more than one active substance, carry out the test for uniformity of delivered dose for each active substance. Unless otherwise justified and authorised, the preparation complies with the test if 9 out of 10 results lie between 75 per cent and 125 per cent of the average value and all lie between 65 per cent and 135 per cent. If 2 or 3 values lie outside the range of 75 per cent to 125 per cent, repeat the test for 2 more inhalers. Not more than 3 of the 30 values lie outside the range 75 per cent to 125 per cent and no value lies outside the range 65 per cent to 135 per cent.

Fine particle dose. Using an apparatus and procedure described in Aerodynamic assessment of fine particles (2.9.18 - apparatus C or D), calculate the fine particle dose. Number of deliveries per inhaler. Take one inhaler and discharge the contents to waste, actuating the valve at intervals of not less than 5 s. The total number of deliveries so discharged from the inhaler is not less than the number stated on the label (this test may be combined with the test for uniformity of delivered dose). Powders for inhalation

DEFINITION
Powders for inhalation are presented as single-dose powders or multidose powders. To facilitate their use, active substances may be combined with a suitable carrier. They are generally administered by dry-powder inhalers. In pre-metered systems, the inhaler is loaded with powders pre-dispersed in capsules or other suitable pharmaceutical forms. For devices using a powder reservoir, the dose is created by a metering mechanism within the inhaler. The delivered dose is the dose delivered from the inhaler. For some preparations, the dose has been established as a metered dose or as a predispensed dose. The metered dose is determined by adding the amount deposited within the device to the delivered dose. It may also be determined directly.

TESTS

Uniformity of delivered dose. In all cases, prepare the inhaler as directed in the instructions to the patient. The dose collection apparatus must be capable of quantitatively capturing the delivered dose. A dose collection apparatus similar to that described for the evaluation of pressurised metered-dose inhalers may be used provided that the dimensions of the tube and the filter can accommodate
Preparations for inhalation

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Figure 0671.-1. – Dose collection apparatus for pressurised metered-dose preparations
Dimensions in millimetres

the measured flow rate. A suitable tube is defined in Figure 0671.-1. Connect the tube to a flow system according to the scheme specified in Figure 0671.-2 and Table 0671.-1.

Unless otherwise stated, determine the test flow rate and duration using the dose collection tube, the associated flow system, a suitable differential pressure meter and a suitable volumetric flow meter, calibrated for the flow leaving the meter, according to the following procedure.

Prepare the inhaler for use and connect it to the inlet of the apparatus using a mouthpiece adapter to ensure an airtight seal. Use a mouthpiece adapter which ensures that the front face of the inhaler mouthpiece is flush with the front face of the sample collection tube. Connect one port of a differential pressure meter to the pressure reading point, P1, in Figure 0671.-2 and let the other be open to the atmosphere. Switch on the pump, open the two way valve and adjust the flow control valve until the pressure drop across the inhaler is 4.0 kPa (40.8 cm H₂O) as indicated by the differential pressure meter. Remove the inhaler from the mouthpiece adapter and without touching the flow control valve, connect a flow meter to the inlet of the sampling apparatus. If the flow rate is above 100 litres/min adjust the flow control valve to obtain a flow rate of 100 ± 5 litres/min. Note the volumetric airflow rate and define this as the test flow rate, Q, in litres per minute. Define the test flow duration, T, in seconds so that a volume of 4 litres of air is drawn through the inhaler.

Ensure that critical flow occurs in the flow control valve by the following procedure. With the inhaler in place and the test flow rate Q, measure the absolute pressure on both sides of the control valve (pressure reading points P2 and P3 in
Preparations for inhalation

**Predispersed systems.** Prepare the inhaler as directed in the instructions to the patient and connect it to the apparatus using an adapter which ensures a good seal. Draw air through the inhaler using the predetermined conditions. Repeat the procedure until the number of deliveries which constitute the minimum recommended dose have been sampled. Quantitatively collect the contents of the apparatus and determine the amount of active substance.

Repeat the procedure for a further 9 doses.

**Reservoir systems.** Prepare the inhaler as directed in the instructions to the patient and connect it to the apparatus using an adapter which ensures a good seal. Draw air through the inhaler under the predetermined conditions. Repeat the procedure until the number of deliveries which constitute the minimum recommended dose have been sampled. Quantitatively collect the contents of the apparatus and determine the amount of active substance.

Repeat the procedure for a further 2 doses.

Discharge the device to waste until \((n/2)+1\) deliveries remain, where \(n\) is the number of deliveries stated on the label. If necessary, store the inhaler to discharge electrostatic charges. Collect 4 doses using the procedure described above.

Discharge the device to waste until 3 doses remain. If necessary, store the inhaler to discharge electrostatic charges. Collect 3 doses using the procedure described above.

For preparations containing more than 1 active substance, carry out the test for uniformity of delivered dose for each active substance.

The preparation complies with the test if 9 out of 10 results lie between 75 per cent and 125 per cent of the average value and all lie between 65 per cent and 135 per cent. If 2 or 3 values lie outside the range of 75 per cent to 125 per cent, repeat the test for 2 more inhalers. Not more than 3 of the 30 values lie outside the range 75 per cent to 125 per cent and no value lies outside the range 65 per cent to 135 per cent.

In justified and authorised cases, these ranges may be extended but no value should be greater than 150 per cent or less than 50 per cent of the average value.

**Fine particle dose.** Using the apparatus and procedure described in *Aerodynamic assessment of fine particles (2.9.18 - apparatus C or D)*, calculate the fine particle dose.

**Number of deliveries per inhaler for multidose inhalers.** Discharge doses from the inhaler until empty, at the predetermined flow rate. Record the deliveries discharged.

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### Table 0671.1 - Specifications of the apparatus described in figure 0671.2

<table>
<thead>
<tr>
<th>Code</th>
<th>Item</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Sample collection tube</td>
<td>Capable of quantitatively capturing the delivered dose, e.g. Dose collection tube similar to that described in Fig. 0671.1 with dimensions of 34.85 mm ID × 12 cm length (e.g. product number XX40 047 00, Millipore Corporation, Bedford, MA 01732 with modified exit tube, ID ≥ 8 mm, fitted with Gelman product number 61633), or equivalent.</td>
</tr>
<tr>
<td>B</td>
<td>Filter</td>
<td>47 mm filter, e.g. A/E glass fibre filter (Gelman Sciences, Ann Arbor, MI 48106), or equivalent.</td>
</tr>
<tr>
<td>C</td>
<td>Connector</td>
<td>ID ≥ 8 mm, e.g. short metal coupling, with low-diameter branch to P1.</td>
</tr>
<tr>
<td>D</td>
<td>Vacuum tubing</td>
<td>8 ± 0.5 mm ID × 50 ± 10 cm length, e.g., silicone tubing with an OD of 14 mm and an ID of 8 mm.</td>
</tr>
<tr>
<td>E</td>
<td>Two-way solenoid valve</td>
<td>Minimum airflow resistance orifice having an ID of ≥ 8 mm and a maximum response time of 100 ms (e.g. type 256-A/08, Bürkert GmbH, D-74653 Ingelfingen), or equivalent.</td>
</tr>
<tr>
<td>F</td>
<td>Vacuum pump</td>
<td>Pump must be capable of drawing the required flow rate through the assembled apparatus with the dry powder inhaler in the mouthpiece adapter (e.g. product type 1023, 1423 or 2565, Gast Manufacturing Inc., Benton Harbor, MI 49022), or equivalent. Connect the pump to the solenoid valve using short and/or wide (≥ 10 mm ID) vacuum tubing and connectors to minimise pump capacity requirements.</td>
</tr>
<tr>
<td>G</td>
<td>Timer</td>
<td>Timer capable of driving the solenoid valve for the required time period (e.g. type G814, RS Components International, Corby, NN17 9RS, UK), or equivalent.</td>
</tr>
<tr>
<td>P1</td>
<td>Pressure tap</td>
<td>2.2 mm ID, 3.1 mm OD, flush with internal surface of the sample collection tube, centre and burr-free, 59 mm from its inlet.</td>
</tr>
<tr>
<td>P1</td>
<td>Pressure measurements</td>
<td>Differential pressure to atmosphere (P1) or absolute pressure (P2 and P3).</td>
</tr>
<tr>
<td>H</td>
<td>Flow control valve</td>
<td>Adjustable regulating valve with maximum Cr ≈ 1, (e.g. type 8FV12LNSS, Parker Hannifin plc., Barnstaple, EX31 1NP, UK), or equivalent.</td>
</tr>
</tbody>
</table>

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**Figure 0671.2.** Apparatus suitable for measuring the uniformity of delivered dose for powder inhalers
The total number of doses delivered is not less than the number stated on the label (this test may be combined with the test for uniformity of delivered dose).

PREPARATIONS FOR IRRIGATION

**Praeparationes ad irrigationem**

**DEFINITION**

Preparations for irrigation are sterile, aqueous large volume preparations intended to be used for irrigation of body cavities, wounds and surfaces, for example during surgical procedures.

Preparations for irrigation are either solutions prepared by dissolving one or more active substances, electrolytes or osmotically active substances in water complying with the requirements for Water for injections (0169) or they consist of such water alone. In the latter case, the preparation may be labelled as water for irrigation. Irrigation solutions are usually adjusted to be isotonic with blood.

Examined in suitable conditions of visibility, preparations for irrigation are clear and practically free from particles.

Preparations for irrigation are supplied in single-dose containers. The containers and closures comply with the requirements for containers for preparations for parenteral use (3.2.1 and 3.2.2) but the administration port of the container is incompatible with intravenous administration equipment and does not allow the preparation for irrigation to be administered with such equipment.

**PRODUCTION**

Preparations for irrigation are prepared using materials and methods designed to ensure sterility and to avoid the introduction of contaminants and the growth of micro-organisms; recommendations on this aspect are provided in the text on Methods of preparation of sterile products (5.1.1).

**TESTS**

**Deliverable mass or volume** (2.9.28). Preparations for irrigation supplied in single-dose containers comply with the test.

**Sterility** (2.6.1). Preparations for irrigation comply with the test for sterility.

**Bacterial endotoxins** (2.6.14): less than 0.5 IU/ml.

**Pyrogens** (2.6.8). Preparations for which a validated test for bacterial endotoxins cannot be carried out comply with the test for pyrogens. Inject per kilogram of the rabbits mass, 10 ml of the preparation, unless otherwise justified and authorised.

**LABELLING**

The label states:

- that the preparation is not to be used for injection,
- that the preparation is to be used for one occasion only and that any unused portion of preparation is to be discarded.

Pressurised pharmaceutical preparations are presented in special containers under pressure of a gas and contain one or more active substances. The preparations are released from the container, upon actuation of an appropriate valve, in the form of an aerosol (dispersion of solid or liquid particles in a gas, the size of the particles being adapted to the intended use) or of a liquid or semi-solid jet such as a foam. The pressure for the release is generated by suitable propellants.

The preparations consist of a solution, an emulsion or a suspension and are intended for local application to the skin or to mucous membranes of various body orifices, or for inhalation. Suitable excipients may also be used, for example solvents, solubilisers, emulsifying agents, suspending agents and lubricants for the valve to prevent clogging.

**Propellants.** The propellants are either gases liquefied under pressure or compressed gases or low-boiling liquids. Liquefied gases are, for example, fluorinated hydrocarbons and low-molecular-mass hydrocarbons (such as propane and butane). Compressed gases are, for example, carbon dioxide, nitrogen and nitrous oxide.

Mixtures of these propellants may be used to obtain optimal solution properties and desirable pressure, delivery and spray characteristics.

**Containers.** The containers are tight and resistant to the internal pressure and may be made of metal, glass, plastic or combinations of these materials. They are compatible with their contents. Glass containers are protected with a plastic coating.

**Spraying device.** The valve keeps the container tightly closed when not in use and regulates the delivery of the contents during use. The spray characteristics are influenced by the type of spraying device, in particular by the dimensions, number and location of orifices. Some valves provide a continuous release, others (“metering dose valves”) deliver a defined quantity of product upon each valve actuation.

The various valve materials in contact with the contents are compatible with them.

**Requirements for pressurised pharmaceutical preparations.** Pressurised preparations are provided with a delivery device appropriate for the intended application.

Special requirements may be necessary for the selection of propellants, for particle size and the single-dose delivered by the metering valves.

**LABELLING**

The label states:

- the method of use,
- any precautions to be taken,