administered in or with water or another suitable liquid. They may also be swallowed directly. They are presented as single-dose or multidose preparations.

Where applicable, containers for oral powders comply with the requirements of *Materials used for the manufacture of containers* (*3.1* and subsections) and *Containers* (*3.2* and subsections).

Multidose oral powders require the provision of a measuring device capable of delivering the quantity prescribed. Each dose of a single-dose powder is enclosed in an individual container, for example a sachet or a vial.

PRODUCTION

In the manufacture of oral powders, means are taken to ensure a suitable particle size with regard to the intended use.

In the manufacture, packaging, storage and distribution of oral powders, suitable means are taken to ensure their microbial quality; recommendations on this aspect are provided in the text on *Microbiological quality of pharmaceutical preparations* (*5.1.4*).

TESTS

Uniformity of dosage units. Single-dose oral powders comply with the test for uniformity of dosage units (*2.9.40*) or, where justified and authorised, with the tests for uniformity of content and/or uniformity of mass shown below. Herbal drugs and herbal drug preparations present in the dosage form are not subject to the provisions of this paragraph.

Uniformity of content (*2.9.6*). Unless otherwise prescribed or justified and authorised, single-dose oral powders with a content of active substance less than 2 mg or less than 2 per cent of the total mass comply with test B for uniformity of content of single-dose preparations. If the preparation has more than one active substance, the requirement applies only to those substances which correspond to the above conditions.

Uniformity of mass (*2.9.5*). Single-dose oral powders comply with the test for uniformity of mass of single-dose preparations. If the test for uniformity of content is prescribed for all the active substances, the test for uniformity of mass is not required.

Uniformity of mass of delivered doses from multidose containers (*2.9.27*). Oral powders supplied in multidose containers comply with the test.

STORAGE

If the preparation contains volatile ingredients, or the contents have to be protected, store in an airtight container.

Effervescent powders

Effervescent powders are presented as single-dose or multidose preparations and generally contain acid substances and carbonates or hydrogen carbonates which react rapidly in the presence of water to release carbon dioxide. They are intended to be dissolved or dispersed in water before administration.

STORAGE

In an airtight container.

01/2008:1037

PREMIXES FOR MEDICATED FEEDING STUFFS FOR VETERINARY USE

Praeadmixta ad alimenta medicata ad usum veterinarium

DEFINITION

Mixtures of one or more active substances, usually in suitable bases, that are prepared to facilitate feeding the active substances to animals. They are used exclusively in the preparation of medicated feeding stuffs.

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.

01/2008:0671

PREPARATIONS FOR INHALATION

Inhalanda

DEFINITION

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, cosolvents, 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,
– 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

3 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 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, dispersions 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 cosolvents 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 they 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 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 on the inhaler to the delivered dose. It may also be determined directly.

TESTS

For breath-operated pressurised metered-dose inhalers, the test conditions described below may need to be modified to ensure that breath actuation occurs for the inhaler under test.

Uniformity of delivered dose. Containers usually operate in a valve-down position. For containers that operate in a valve-up 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 (Figure 0671.-1) and procedure may be used.

The apparatus 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 or the 2.5 mm indented shoulder of the sample collection tube, as appropriate. 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 litres/min (± 5 per cent). 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

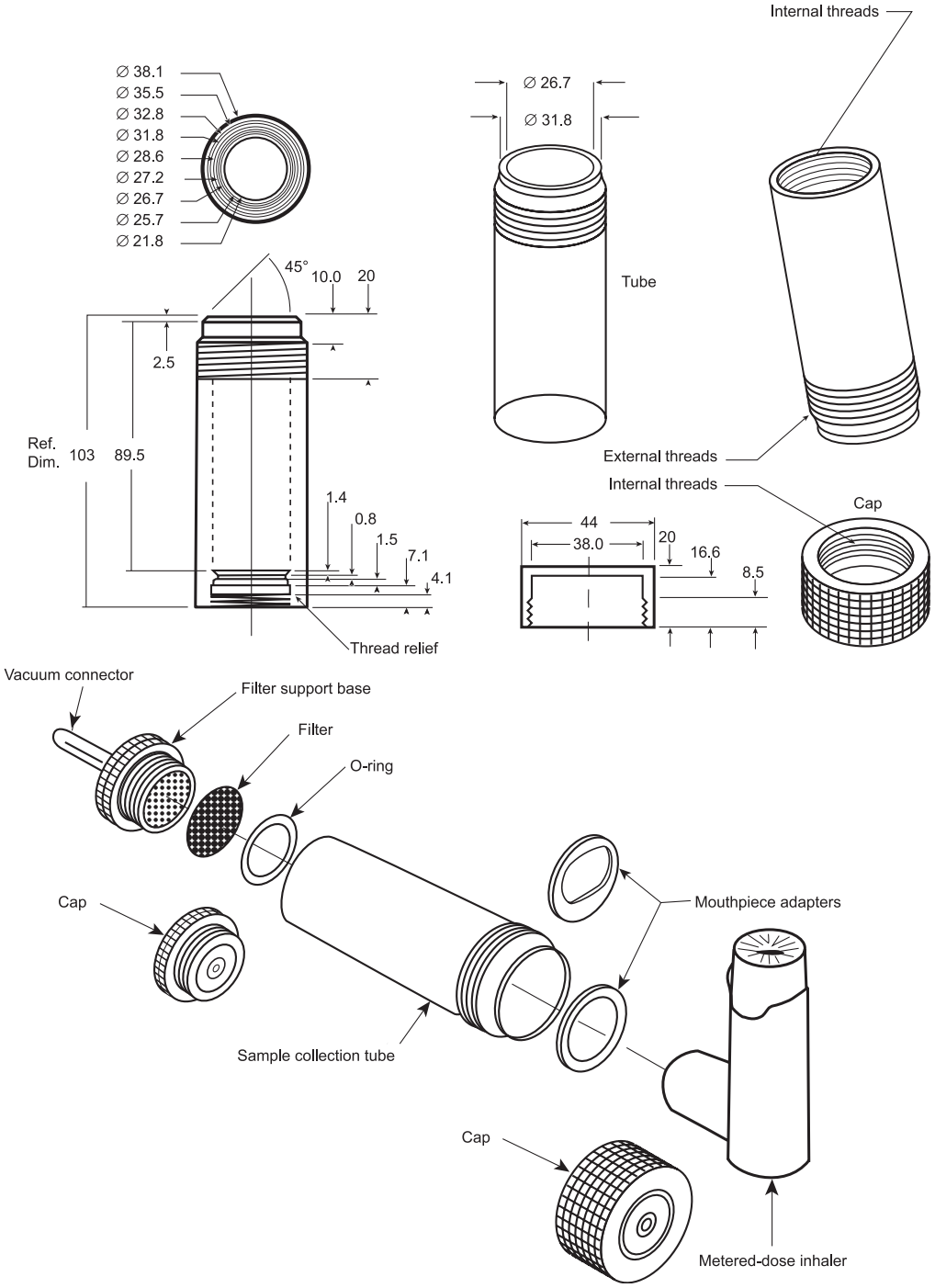

Figure 0671.-1. – *Dose collection apparatus for pressurised metered-dose inhalers*
Dimensions in millimetres

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 $(n/2)+1$ 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 limits 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 limits of 75 per cent to 125 per cent and no value lies outside the limits of 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, D or E*), 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 powder inhalers. For pre-metered inhalers, the inhaler is loaded with powders pre-dispensed in capsules or other suitable pharmaceutical forms. For inhalers 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 on the inhaler 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 the measured flow rate. A suitable tube is defined in Table 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 flowmeter, 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 2-way solenoid valve and adjust the flow control valve until the pressure drop across the inhaler is 4.0 kPa (40.8 cm H_2O) as indicated by the differential pressure meter. Remove the inhaler from the mouthpiece adapter and without touching the flow control valve, connect a flowmeter to the inlet of the sampling apparatus. Use a flowmeter calibrated for the volumetric flow leaving the meter, or calculate the volumetric flow leaving the meter (Q_{out}) using the ideal gas law. For a meter calibrated for the entering volumetric flow (Q_{in}), use the following expression:

$$Q_{out} = \frac{Q_{in} \times P_0}{P_0 - \Delta P}$$

P_0 = atmospheric pressure,

ΔP = pressure drop over the meter.

If the flow rate is above 100 litres/min adjust the flow control valve to obtain a flow rate of 100 litres/min (± 5 per cent). Note the volumetric airflow rate exiting the meter and define this as the test flow rate, Q_{out}, in litres per minute. Define the test flow duration, T, in seconds so that a volume of 4 litres of air is drawn from the mouthpiece of the inhaler at the test flow rate, Q_{out}.

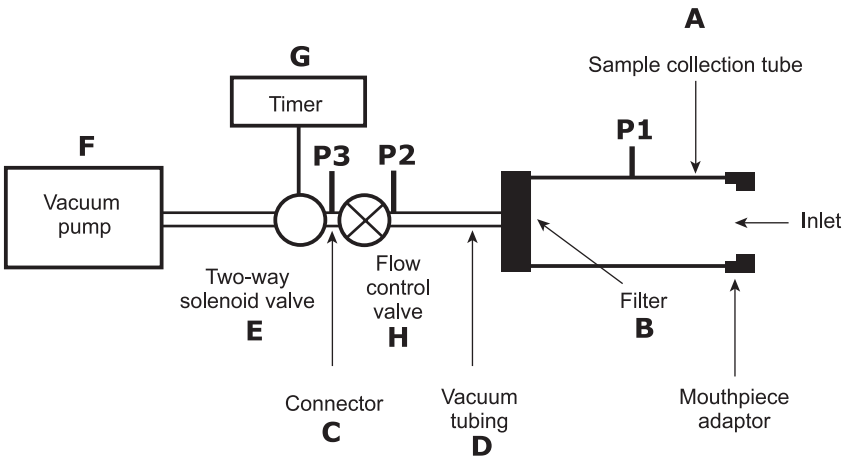

Figure 0671.-2. – *Apparatus suitable for measuring the uniformity of delivered dose for powder inhalers*

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_{out}, measure the absolute pressure on both sides of the control valve (pressure reading points P2 and P3 in Figure 0671.-2). A ratio P3/P2 of less than or equal to 0.5 indicates critical flow. Switch to a more powerful pump and re-measure the test flow rate if critical flow is not indicated.

Table 0671.-1. – *Specifications of the apparatus used for powder inhalers described in Figure 0671.-2*

Code	Item	Description
A	Sample collection tube	Capable of quantitatively capturing the delivered dose, e.g. dose collection tube similar to that described in Figure 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 61631), or equivalent.
B	Filter	47 mm filter, e.g. A/E glass fibre filter (Gelman Sciences, Ann Arbor, MI 48106), or equivalent.
C	Connector	ID ≥ 8 mm, e.g., short metal coupling, with low-diameter branch to P3.
D	Vacuum tubing	A length of suitable tubing having an ID ≥ 8 mm and an internal volume of 25 ± 5 ml.
E	2-way solenoid valve	A 2-way, 2-port solenoid valve having a minimum airflow resistance orifice with ID ≥ 8 mm and an opening time ≤ 100 ms (e.g. type 256-A08, Bürkert GmbH, D-74653 Ingelfingen), or equivalent.
F	Vacuum pump	Pump must be capable of drawing the required flow rate through the assembled apparatus with the 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 2-way solenoid valve using short and/or wide (≥ 10 mm ID) vacuum tubing and connectors to minimise pump capacity requirements.
G	Timer	Timer capable of driving the 2-way solenoid valve for the required time period (e.g. type G814, RS Components International, Corby, NN17 9RS, UK), or equivalent.
P1	Pressure tap	2.2 mm ID, 3.1 mm OD, flush with internal surface of the sample collection tube, centred and burr-free, 59 mm from its inlet. The pressure tap P1 must never be open to the atmosphere.
P1 P2 P3	Pressure measurements	Differential pressure to atmosphere (P1) or absolute pressure (P2 and P3).
H	Flow control valve	Adjustable regulating valve with maximum $Cv \geq 1$, (e.g. type 8FV12LNSS, Parker Hannifin plc., Barnstaple, EX31 1NP, UK), or equivalent.

Predispensed 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 one active substance, carry out the test for uniformity of delivered dose for each active substance.

Results. 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 limits 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 limits of 75 per cent to 125 per cent and no value lies outside the limits of 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, D or E*), 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. 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).

01/2008:1116

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 make the preparation isotonic with respect to 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