EAG/Panel/Working Party	Medicinal Chemicals 2
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Deadline for Comment	31 March 2018
Notes: Draft revised monograph. Updated Identification, Uniformity of Delivered Dose, Related substances and Assay tests.	

Salbutamol Pressurised Inhalation, Suspension

Salbutamol Pressurised Inhalation

Salbutamol Preparations

Action and use
Beta$_2$-adrenoceptor agonist; bronchodilator.

DEFINITION

Salbutamol Pressurised Inhalation, Suspension is a suspension of either Salbutamol or Salbutamol Sulfate in a suitable liquid in a pressurised container fitted with a metering dose valve.

The pressurised inhalation, suspension complies with the requirements stated under Preparations for Inhalation and with the following requirements.

PRODUCTION

The size of aerosol particles to be inhaled is controlled so that a consistent portion is deposited in the lungs. The fine-particle characteristics of preparations for inhalation are determined using the method described in Appendix XII C7. Preparations for inhalation: Aerodynamic Assessment of Fine Particles. The test and limits should be agreed with the competent authority.

The water content is controlled to ensure the performance of the product as justified and authorised by the competent authority.

Content of salbutamol, $C_{13}H_{21}NO_3$
85.0 to 115.0% of the stated delivered dose (ex-actuator).

IDENTIFICATION

The *infrared absorption spectrum*, Appendix II A, in the range 1650 to 400 cm^{-1} is concordant with the *reference spectrum* of either salbutamol (*RS 314*) or salbutamol sulfate (*RS 315*), as appropriate. Examine the substance as a dispersion in *potassium bromide* prepared in the following manner. Discharge the inhaler a sufficient number of times into a mortar to obtain 2 mg of Salbutamol, grind the residue thoroughly with 0.1 g of *potassium bromide*, add a further 0.2 g of *potassium bromide* and mix thoroughly.

TESTS

Uniformity of delivered dose
Complies with the requirements stated under Pressurised Metered-dose Preparations for Inhalation using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Collect single doses of the preparation being examined using the procedure described under Pressurised Metered-dose Preparations for Inhalation, Uniformity of delivered dose and dissolve the collected dose in sufficient *methanol* to produce a solution containing the equivalent of 0.000075% w/v of Salbutamol.

(2) 0.00018% w/v of *salbutamol sulfate BPCRS* in *methanol.*

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm x 3 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.85 mL per minute.

(d) Use a column temperature of 50º.

(e) Use a detection wavelength of 276 nm.

(f) Inject 150 µL of each solution

MOBILE PHASE

762 volumes of *methanol* and 238 volumes of 0.1% w/v of *ammonium acetate solution*.

DETERMINATION OF CONTENT

Calculate the content of Salbutamol, $C_{13}H_{21}NO_3$ per aliquot of solvent using the declared content of $C_{13}H_{21}NO_3$ in *salbutamol sulfate BPCRS*. Repeat the procedure as described under Pressurised Metered-dose Preparations for Inhalation, Uniformity of delivered dose.

Related substances
Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) Shake a quantity of the pressurised inhalation containing 5 mg of Salbutamol with 25 mL of *water* to produce a solution containing 0.02% w/v of salbutamol.

(2) Dilute 1 volume of solution (1) to 100 volumes with *water*.

(3) 0.005% w/v of *salbutamol sulfate for system suitability EPCRS*, 0.005% w/v of 2-*tert-butylamino-1-(4-hydroxy-3-methylphenyl)ethanol BPCRS* (impurity C) and 0.00075% w/v of *salbutamol ketone impurity BPCRS* (impurity J) in *water*.

(4) Dilute 1 volume of solution (2) to 10 volumes with *water*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *end-capped octylsilyl silica gel for chromatography* (5 µm) (Hypersil 100 C8 is suitable).

(b) Use gradient elution and the mobile phase described below.

(c) Use a flow rate of 1.0 mL per minute.
(d) Use a column temperature of 30º.
(e) Use a detection wavelength of 273 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A 0.1M ammonium acetate, adjusted to pH 4.5 with *acetic acid*
Mobile phase B isopropranol.

Time (Min)	Mobile Phase A (% v/v)	Mobile phase B (% v/v)	Comment
0 – 5	96	4	isocratic
5 – 20	96 – 86	4 – 14	linear gradient
20 – 30	86	14	isocratic
30 – 31	86 – 96	14 – 4	linear gradient
31 – 45	96	4	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to salbutamol (retention time of about 6.4 minutes) are: impurity J, about 0.9; impurity C, about 2.1; impurity D, about 2.3, impurity N, about 2.5 and impurity F, about 2.6.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to salbutamol and salbutamol ketone is at least 1.0.

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity N and impurity F is at least 1.2.

LIMITS

Use the chromatogram obtained with solution (3) to identify the peaks due to impurities C, D, F, J and N in the chromatogram obtained from solution (1). Multiply the area of any peak corresponding to impurity C, F, J and N by a correction factor of 1.7, 0.6, 0.2 and 1.4 respectively.

In the chromatogram obtained with solution (1):

the area of any *secondary peak* is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the sum of the areas of all *secondary peaks* is not greater than 1.2 times the area of the principal peak in the chromatogram obtained with solution (2) (1.2%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

ASSAY

Use the average of the individual results determined in the test for Uniformity of delivered dose.

LABELLING

The label states the content of active ingredient in terms of the equivalent amount of salbutamol.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Salbutamol.