AEROSOL FORMULATION FOR COPD

FIELD OF THE INVENTION

The present invention relates to pharmaceutical aerosol solution formulations comprising glycopyrronium bromide, intended for use in pressurized metered dose inhalers. The invention further relates to use of such formulations in the prevention and therapy of respiratory disorders, including COPD.

BACKGROUND OF THE INVENTION

Glycopyrronium bromide (also known as glycopyrrolate) is a muscarinic M3 anticholinergic agent used to reduce salivation associated with administration of certain anaesthetics, and as adjunctive therapy for peptic ulcers. It has also been reported to be effective in the treatment of asthmatic symptoms (Hansel et al., Chest 2005; 128:1974-1979).

WO 2005/107873 relates to use of glycopyrrolate for the treatment of childhood asthma.

WO 01/76575 discloses a controlled release formulation for pulmonary delivery of glycopyrrolate. The formulation is intended for use in treatment of respiratory disease, in particular chronic obstructive pulmonary disease (COPD). The application focuses on dry powder formulations suitable for delivery by means of a dry powder inhaler (DPI).

One of the drawbacks of DPIs is that insufficient patient inhalation flow rates may lead to reduced dose delivery and incomplete deaggregation of the powder, leading to unsatisfactory device performance. For this reason DPIs are normally used only in older children and adults. Younger children and other people with inhalation difficulties can benefit from use of propellant-based aerosol formulations, administered by pressurized metered dose inhalers (pMDIs). pMDIs use propellant to expel droplets containing the

pharmaceutical product to the respiratory tract in an aerosol.

It would be desirable to provide a clinically useful aerosol product in the form of a solution that delivers the therapeutic benefits of glycopyrronium bromide in effective and consistent doses over an extended product lifetime, and ideally without the need for storage under special conditions of temperature or humidity.

SUMMARY OF THE INVENTION

The present invention provides a pharmaceutical composition comprising glycopyrronium bromide dissolved in an HFA propellant, an optional co-solvent, and an amount of acid sufficient to stabilize the glycopyrronium bromide. Additional pharmaceutically active ingredients may also be included.

In a further aspect the invention provides a pressurized metered dose inhaler or other container suitable for aerosol delivery, comprising the pharmaceutical composition of the invention.

In another aspect the invention provides the use of pharmaceutical compositions as described herein for the therapeutic or palliative treatment or prevention of respiratory disease conditions, such as COPD.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

A solution formulation of glycopyrronium bromide in HFA propellant with ethanol as co-solvent was prepared and checked for stability after 3 months following storage under different conditions of temperature and humidity. One batch was stored under optimal conditions (refrigeration); the other batches were stored under accelerated degradation conditions of high temperature and humidity. Although the refrigerated batch remained stable over the 3 month period, the other batches degraded significantly over that time-span. This is the first time that glycopyrronium bromide has been

observed to exhibit poor stability in any type of formulation.

Thus, a simple aerosol solution formulation of glycopyrronium bromide dissolved in propellant and co-solvent fails to meet the requirements for practical use, namely that it should be capable of being carried on the person without refrigeration and yet deliver consistent dosages of active ingredient.

The present inventors were able to overcome these stability issues by inclusion of a specific amount of inorganic acid in the formulation. In particular, they found that inclusion of an amount of 1M hydrochloric acid (HCl) in the range of 0.005-1.0 μg/μl, preferably 0.099-0.74 μg/μl, and more preferably 0.18-0.32 μg/μl, to the solution is sufficient to eliminate degradation of glycopyrronium bromide over an extended period of non-optimal storage, thereby ensuring a consistent dose of glycopyrronium bromide per actuation of the pMDI containing the solution formulation.

Glycopyrronium bromide, chemically defined as 3-[(cyclopentylhydroxyphenylacetyl)oxy]-1,1-dimethylpyrrolidinium bromide, has two chiral centres corresponding to four potential different stereoisomers with configurations (3R,2'R)-, (3S,2'R)-, (3R,2'S)- and (3S,2'S)-. Glycopyrronium bromide in the form of any of these pure enantiomers or diastereomers or any combination thereof may be used in practising the present invention. In one embodiment of the invention the (3S,2'R),(3R,2'S)-3-[(cyclopentylhydroxyphenylacetyl)oxy]-1,1-dimethylpyrrolidinium bromide racemic mixture, also known as glycopyrrolate is preferred. Glycopyrronium bromide is present in the formulation in an amount in the range from 0.005 to 0.14% (w/w), preferably from 0.010 to 0.13% (w/w), more preferably from 0.015 to 0.04% (w/w), wherein% (w/w) means the amount by weight of the component, expressed as percent with respect to the total weight of the composition.

Glycopyrrolate is commercially available, and can be synthesized

according to the process described in US 2,956,062 or in Franko BV and Lunsford CD, J Med Pharm Chem 2(5), 523-540, 1960.

The propellant component of the composition may be any pressure-liquefied propellant and is preferably a hydrofluoroalkane (HFA) or a mixture of different HFAs, more preferably selected from the group consisting of HFA134a (1,1,1,2-tetrafluoroethane), HFA 227 (1,1,1,2,3,3,3-heptafluoropropane, and mixtures thereof. The preferred HFA is HFA134a. HFAs may be present in the formulation in an amount in the range from 75 to 95% (w/w), preferably from 85 to 90% (w/w).

The co-solvent incorporated into formulation of the invention has a higher polarity than that of the propellant and may include one or more substances such as a pharmaceutically acceptable alcohol, in particular ethanol, or a polyol such as propylene glycol or polyethylene glycol.

Advantageously the co-solvent is selected from the group of lower branched or linear alkyl (C_1-C_4) alcohols such as ethanol and isopropyl alcohol. Preferably the co-solvent is ethanol.

The concentration of the co-solvent will vary depending on the final concentration of the active ingredient in the formulation and on the type of propellant. For example ethanol may be used in a concentration comprised in the range from 5 to 25% (w/w), preferably from 8 to 20% (w/w), more preferably from 10 to 15% (w/w). In one of the preferred embodiments the concentration of ethanol is 12% (w/w).

The ratio of propellant to co-solvent in the formulation is preferably in the range 50:50 to 95-5 (w/w).

It is envisaged that HCl of different molarity or alternative inorganic acids (mineral acids) could substitute for 1M HCl in the formulations of the invention. For instance, alternative acids could be any pharmaceutically acceptable monoprotic or polyprotic acid, such as (but not limited to):

hydrogen halides (hydrochloric acid hydrobromic acid, hydroiodic acid etc.) phosphoric acid, nitric acid, sulphuric acid, and halogen oxoacids.

The pharmaceutically active components of the composition are preferable completely and homogeneously dissolved in the mixture of propellant and co-solvent, i.e. the composition is preferably a solution formulation.

Optionally the solution formulation compositions may comprise other pharmaceutical excipients or additives known in the art. In particular, the compositions of the invention may comprise one or more low volatility components. Low volatility components are useful in order to increase the mass median aerodynamic diameter (MMAD) of the aerosol particles upon actuation of the inhaler and/or to improve the solubility of the active ingredient in the propellant/co-solvent mixture.

The low volatility component, when present, has a vapour pressure at 25°C lower than 0.1 kPa, preferably lower than 0.05 kPa. Examples of low-volatility components may be esters such as isopropyl myristate, ascorbyl myristate, tocopherol esters; glycols such as propylene glycol, polyethylene glycol, glycerol; or surface active agents such as a saturated organic carboxylic acid (i.e. lauric, myristic, stearic acid) or an unsaturated carboxylic acid (i.e. oleic or ascorbic acid).

The amount of low volatility component may vary from 0.1 to 10% w/w, preferably from 0.5 to 5% (w/w), more preferably between 1 and 2% (w/w).

In one embodiment of the invention an amount of water comprised between 0.005 and 0.5% (w/w) may optionally be added to the formulations in order to favourably affect the solubility of the active ingredient without increasing the MMAD of the aerosol droplets upon actuation.

Advantageously, the formulations of the invention are free of excipients

(such as surfactants) other than the co-solvent, the propellant and a stabilizing amount of an acid.

The invention also relates to a method for preparing a pharmaceutical composition, comprising adding 1M HCl or to a solution of glycopyrronium bromide in HFA propellant and co-solvent, wherein the amount of 1M HCl added is in the range of 0.005-1.0 μg per μl of the final solution.

The pharmaceutical compositions of the invention may further comprise other, additional pharmaceutically active agents for separate, sequential or simultaneous use. Optional additional pharmaceutically active components of the composition include any known in the art for prophylaxis or treatment of respiratory diseases and their symptoms. Examples of these active components are: beta-2-agonists such as formoterol, salbutamol, fenoterol, carmoterol (TA 2005), indacaterol, milveterol, vilanterol (GSK 642444), terbultaline, salmeterol, bitolterol, metaproterenol all in form of single stereoisomers or mixtures thereof and salts thereof; corticosteroids such as beclometasone dipropionate, fluticasone propionate, butixocort, mometasone furoate, triamcinolone acetonide, budesonide and its 22R-epimer, ciclesonide, flunisolide, loteprednol, and rofleponide; other anti-muscarinic drugs such as methscopolamine, ipratropium bromide, oxitropium bromide and tiotropium bromide; phosphodiesterase IV inhibitors such as: cilomilast, roflumilast and tetomilast. Among these additional active components formoterol fumarate is particularly preferred.

The compositions of the invention can be inhaled from any suitable MDI device known to the skilled person. Desired doses of the individual pharmaceutically active components of the formulation are dependent on the identity of the component and the type and severity of the disease condition, but are preferably such that a therapeutic amount of the active ingredient is delivered in one or two actuations. Generally speaking, doses of active

ingredient are in the range of about 0.5 μg-1000 μg per actuation, e.g. about 1-100 μg/actuation, and sometimes about 5-50 μg/actuation. The skilled person in the field is familiar with how to determine the appropriate dosage for each individual pharmaceutically active ingredient.

With specific reference to glycopyrronium bromide, the preferred dosage is about 0.5-100 μg per actuation, preferably about 1-40 μg per actuation, more preferably about 5-26 μg per actuation, even more preferably 25 μg per actuation.

The pharmaceutical formulation of the invention is filled into pMDI devices known in the art. Said devices comprise a canister fitted with a metering valve. Actuation of the metering valve allows a small portion of the spray product to be released.

Part or all of the canister may be made of a metal, for example aluminium, aluminium alloy, stainless steel or anodized aluminium. Alternatively the canister may be a plastic can or a plastic-coated glass bottle.

The metal canisters may have part or all of the internal surfaces lined with an inert organic coating. Examples of preferred coatings are epoxy-phenol resins, perfluorinated polymers such as perfluoroalkoxyalkane, perfluoroalkoxyalkylene, perfluoroalkylenes such as poly-tetrafluoroethylene (Teflon), fluorinated-ethylene-propylene (FEP), polyether sulfone (PES) or fluorinated-ethylene-propylene polyether sulfone (FEP-PES) mixtures or combination thereof. Other suitable coatings could be polyamide, polyimide, polyamideimide, polyphenylene sulfide or their combinations.

In certain embodiments canisters having the internal surface lined with FEP-PES or Teflon may preferably be used.

In other particular embodiments canisters made of stainless steel may be used.

The container is closed with a metering valve for delivering a daily

therapeutically effective dose of the active ingredient. Generally the metering valve assembly comprises a ferrule having an aperture formed therein, a body moulding attached to the ferrule which houses the metering chamber, a stem consisting of a core and a core extension, an inner- and an outer- seal around the metering chamber, a spring around the core, and a gasket to prevent leakage of propellant through the valve.

The gasket seal and the seals around the metering valve may comprise elastomeric material such as EPDM, chlorobutyl rubber, bromobutyl rubber, butyl rubber, or neoprene. EPDM rubbers are particularly preferred. The metering chamber, core and core extension are manufactured using suitable materials such as stainless steel, polyesters (e.g. polybutyleneterephthalate (PBT)), or acetals. The spring is manufactured in stainless steel eventually including titanium. The ferrule may be made of a metal, for example aluminum, aluminum alloy, stainless steel or anodized aluminum. Suitable valves are available from manufacturers such as Valois, Bespak plc and 3M-Neotechnic Ltd.

The pMDI is actuated by a metering valve capable of delivering a volume of between 25-100 μl, preferably between 40-70 μl, and optionally about 50 μl, or about 63 μl per actuation.

Each filled canister is conveniently fitted into a suitable channeling device prior to use to form a metered dose inhaler for administration of the medicament into the lungs of a patient. Suitable channeling devices comprise, for example, a valve actuator and a cylindrical or cone-like passage through which medicament may be delivered from the filled canister via the metering valve to the mouth of a patient e.g. a mouthpiece actuator.

In a typical arrangement the valve stem is seated in a nozzle block which has an orifice leading to an expansion chamber. The expansion chamber has an exit orifice which extends into the mouthpiece. Actuator (exit) orifices

having a diameter in the range 0.15 - 0.45 mm and a length from 0.30 to 1.7 mm are generally suitable. Preferably an orifice having a diameter from 0.2 to 0.44 mm is used, e.g. 0.22, 0.25, 0.30, 0.33 or 0.42 mm.

In certain embodiments of the invention, it may be useful to utilize actuator orifices having a diameter ranging from 0.10 to 0.22 mm, in particular from 0.12 to 0.18 mm, such as those described in WO 03/053501. The use of said fine orifices may also increase the duration of the cloud generation and hence, may facilitate the coordination of the cloud generation with the slow inspiration of the patient.

In case the ingress of water into the formulation is to be avoided, it may be desired to overwrap the MDI product in a flexible package capable of resisting water ingress. It may also be desirable to incorporate a material within the packaging which is able to adsorb any propellant and co-solvent which may leak from the canister (e.g. a molecular sieve).

Optionally the MDI device filled with the formulation of the invention may be utilized together with suitable auxiliary devices favoring the correct use of the inhaler. Said auxiliary devices are commercially available and, depending on their shape and size, are known as "spacers", "reservoirs" or "expansion chambers". Volumatic™ is, for instance, one of the most widely known and used reservoirs, while Aerochamber™ is one of the most widely used and known spacers. A suitable expansion chamber is reported for example in WO 01/49350.

The formulation of the invention may also be used with common pressurized breath-activated inhalers such as those known with the registered names of Easi-Breathe™ and Autohaler™.

The efficacy of an MDI device is a function of the dose deposited at the appropriate site in the lungs. Deposition is affected by the aerodynamic particle size distribution of the formulation which may be characterised in

vitro through several parameters.

The aerodynamic particle size distribution of the formulation of the invention may be characterized using a Cascade Impactor according to the procedure described in the European Pharmacopoeia 6th edition, 2009 (6.5), part 2.09.18. An Apparatus E, operating at a flow rate range of 30 litres/min to 100 litres/min or an Apparatus D -Andersen Cascade Impactor (ACI)-, operating at a flow rate of 28.3 l/min, may be utilized. Deposition of the drug on each ACI plate is determined by high performance liquid chromatography (HPLC).

The following parameters of the particles emitted by a pressurized MDI may be determined:

i) mass median aerodynamic diameter (MMAD) is the diameter around which the mass aerodynamic diameters of the emitted particles are distributed equally;

ii) delivered dose is calculated from the cumulative deposition in the ACI, divided by the number of actuations per experiment;

iii) respirable dose (fine particle dose = FPD) is obtained from the deposition from Stages 3 (S3) to filter (AF) of the ACI, corresponding to particles of diameter $\leq$ 4.7 microns, divided by the number of actuations per experiment;

iv) respirable fraction (fine particle fraction=FPF) which is the percent ratio between the respirable dose and the delivered dose.

v) "superfine" dose is obtained from the deposition from Stages 6 (S6) to filter, corresponding to particles of diameter $\leq$ 1.1 microns, divided by the number of actuations per experiment.

The solutions of the invention are capable of providing, upon actuation of the pMDI device in which they are contained, a total FPF higher than 40%, preferably higher than 50%, more preferably higher than 60%.

Moreover the formulations of the invention are capable of providing, on actuation, a fraction higher than or equal to 30% of emitted particles of diameter equal to or less than 1.1 microns as defined by the content stages S6-AF of an Andersen Cascade Impactor, relative to the total fine particle dose collected in the stages S3-AF of the impactor. Preferably the fraction of emitted particles of diameter equal to or less than 1.1 microns is higher than or equal to 40%, more preferably higher than 50%, even more preferably higher than 60%, most preferably higher than 70%.

According to a further aspect of the invention there is provided a method of filling an aerosol inhaler with a composition of the invention. Conventional bulk manufacturing methods and machinery well known to those skilled in the art of pharmaceutical aerosol manufacture may be employed for the preparation of large-scale batches for the commercial production of filled canisters.

The method comprises:

a) preparing a solution comprising glycopyrronium bromide, a co-solvent (e.g. ethanol), a mineral acid, a propellant comprising a HFA and optionally a low volatility component at a temperature from -50 to -60°C at which the solution does not vaporize;

b) cold filling the inhaler with the prepared solution; and

c) placing the valve onto the can and crimping.

An alternative method comprises:

a) preparing a solution comprising glycopyrronium bromide, a co-solvent (e.g. ethanol), a mineral acid, and optionally a low volatility component;

b) filling the open can with the bulk solution;

c) placing the valve onto the can and (vacuum) crimping; and

d) pressure-filling the can with HFA propellant through the valve.

A further alternative method comprises:

a) preparing a solution comprising glycopyrronium bromide, a co-solvent (e.g. ethanol), a mineral acid, an optional low volatility component and HFA propellant using a pressurised vessel:

b) placing the valve onto the empty can and crimping; and

c) pressure-filling the can with the final solution formulation through the valve.

The packaged formulations of the invention are stable for extended periods of time when stored under normal conditions of temperature and humidity. In a preferred embodiment the packaged formulations are stable for at least 6 months at 25°C and 60% RH, more preferably for at least 1 year, most preferably for at least 2 years. Stability is assessed by measuring content of residual active ingredient. A "stable" formulation as defined herein means one retaining at least about 85%, preferably at least about 90%, and most preferably at least about 95% of residual content of each active ingredient at a given time point, as measured by HPLC-UV VIS.

The optimized stable formulations meet the specifications required by the ICH Guideline Q1B or CPMP/QWP/122/02 Rev.1 relevant for drug product stability testing for the purposes of drug registration.

The product of the invention may be used for prophylactic purposes or for symptomatic relief of a wide range of respiratory disorders, such as asthma of all types and chronic obstructive pulmonary disease (COPD).

Other respiratory disorders for which use of the pharmaceutical compositions of the invention may be beneficial are those characterized by obstruction of the peripheral airways as a result of inflammation and presence of mucus, such as chronic obstructive bronchiolitis, chronic bronchitis, emphysema, acute lung injury (ALI), cystic fibrosis, rhinitis, and adult or acute respiratory distress syndrome (ARDS).

EXAMPLES

Example 1: Glycopyrronium bromide stability during storage with or without acid addition

Solution formulations were prepared with the compositions shown in Table 1.

Table 1: Composition of the tested Gly pMDI solution formulations

	Theoretical Unit Formula (μg/actuation for a 63 μl valve)				
	Glycopyrronium bromide (GLY)	**Anhydrous ethanol**	**1M HCl**	**HFA 134a**	**Total**
Without Acid	25	8856	-	64919	73800
With Acid	25	8856	14	64905	73800

The samples containing acid were formulated by the addition of 1M HCl in an amount corresponding to 0.222 μg/μl of the solution.

The solution was filled into canisters which were stored inverted under different conditions: 5°; 25°C/60% RH; 30°C/ 75% RH; 40°C/ 75%RH. The samples were analyzed chromatographically for glycopyrronium bromide content after 1-3 months of storage and after 6 months storage only for 5°; 25°C/60% RH. The results are reported in the following Table 2.

Table 2: GLY pMDI can content (mean% residue ± standard deviation)

Temperature/ relative humidity	Glycopyrronium Bromide (without acid)				Glycopyrronium Bromide (with acid)			
	1M	2M	3M	6M	1M	2M	3M	6M
5°C	98.4±0.9	99.9±1.3	99.3±2.1	99.6±0.4	102.8±1.1	101.4±0.5	103.3±0.4	103.5 ±0.4
25°C/60%	93.8±1.4	91.3±0.7	90.3±1.1	84.2±0.2	101.7±0.7	101.9±0.5	102.7±0.0	102.8 ±0.4
30°C/75%	90.5±4.2	87.8±1.8	88.9±2.3	-	101.1±1.2	100.7±0.0	102.3±0.4	-
40°C/75%	92.5±3.1	88.4±4.7	80.2±1.9	-	100.1±2.4	101.8±0.4	102.0±1.4	-

As shown in Table 2, GLY was relatively unstable when stored under suboptimal conditions. After 3 months at 40°C/75% RH the content of GLY in the samples decreased to about 80%. However, in the presence of acid there was no significant degradation of GLY at 3 months, irrespective of the storage conditions. The obtained data at 5°; 25°C/60% RH show that in presence of acid the product can be stored both in normal and accelerated conditions whereas without acid it is not possible to store it at 25°C/60% RH

Example 2: Glycopyrronium bromide stability during storage with different amount of HCl

Solution formulations were prepared with a composition corresponding to that of Example 1, Table 1, added with the following different amounts of 1 M HCl:

1M HCl

µg/actuation (for a 63 µl valve)	µg/µl of the formulation
0.312	0.0050
3.13	0.0497
6.25	0.0992
11.8	0.187
15.6	0.248
20.6	0.327
25.0	0.397
28.1	0.446
46.8	0.743
65.6	1.041

The solutions were filled into conventional aluminium canisters provided with EPDM valves which were stored inverted for 1 month at 40°C/75%RH. The samples were analyzed chromatographically for glycopyrronium bromide content and the values are the mean values from three cans.

No stability issues were found for the whole range of acid concentrations.

The residual glycopyrronium bromide content ranged from 95.9±0.5% to 101.9±2.4% with respect to the content at time 0 and the total degradation product ranged from 0.8 ± 0.1 to 3.7 ± 1.0% of the total composition. Moreover when the concentrations of the acid was lower than 0.187 µg/µl or higher than 0.743 µg/µl less residual active ingredient, higher levels of degradation products and more variability of their levels were obtained.

Therefore stable glycopyrronium bromide HFA solution formulations may be obtained by using an amount of 1M hydrochloric acid (HCl) in the range of 0.005-1.0 µg/µl, preferably of 0.099-0.74 µg/µl, and more preferably 0.18-0.32 µg/µl.

CLAIMS

1. A pharmaceutical composition comprising glycopyrronium bromide at a dosage in the range of 0.5-100 μg per actuation dissolved in an HFA propellant and a co-solvent, characterised in that said composition contains an amount of 1M hydrochloric acid (HCl) in the range of 0.005-1.0 μg/μl.

2. A composition according to claim 1 wherein the range of 1M HCl is 0.18 - 0.32 μg/μl.

3. A composition according to claim 1 or claim 2 wherein the co-solvent is ethanol.

4. A composition according to any preceding claim wherein glycopyrronium bromide is at dosage in the range 1-40 μg per actuation.

5. A composition according to any preceding claim wherein glycopyrronium bromide is at a dosage in the range 5-26 μg per actuation.

6. A composition according to any preceding claim wherein glycopyrronium bromide is at a dosage of 25 μg per actuation.

7. A composition according to any preceding claim that additionally comprises one or more pharmaceutically active ingredients selected from the group consisting of beta-2-agonists, corticosteroids, antimuscarinic agents, and phosphodiesterase (IV) inhibitors.

8. A composition according to claim 7 wherein the additional one or more pharmaceutical active ingredient is selected from the group of the beta-2-agonists and is represented by formoterol fumarate.

9. A composition according to claim 7 or claim 8 wherein the additional one or more pharmaceutical active ingredient is selected from the group of the corticosteroids and is represented by beclometasone dipropionate.

10. A metered dose inhaler comprising a pharmaceutical composition as defined in any preceding claim.

11. A kit-of-parts comprising the pharmaceutical composition as defined in claim 1 and further comprising one or more pharmaceutically active ingredients for separate, sequential or simultaneous administration, wherein said pharmaceutically active ingredients are selected from the group consisting of beta-2-agonists, corticosteroids, antimuscarinic agents, and phosphodiesterase (IV) inhibitors.

12. Use of a pharmaceutical composition as defined in any of claims 1 to 9 in the manufacture of a medicament for use in the treatment or prophylaxis of a respiratory disease, such as asthma and COPD.

13. A pharmaceutical composition according to any of claims 1 to 9 for use in the prevention or treatment of asthma and COPD.

14. A method of filling an aerosol canister with the pharmaceutical composition as defined in any of claims 1 to 9, comprising the steps of:

a) preparing a solution comprising glycopyrronium bromide, a co-solvent, a mineral acid and optionally a low volatility component;

b) filling the open canister with the solution;

c) placing the valve onto the canister and crimping; and

d) pressure-filling the canister with HFA propellant through the valve.