



- (51) **International Patent Classification:**  
*A61M 15/08* (2006.01) *A61M 15/00* (2006.01)
- (21) **International Application Number:**  
PCT/EP2013/053746
- (22) **International Filing Date:**  
25 February 2013 (25.02.2013)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**  
61/603,095 24 February 2012 (24.02.2012) US
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(81) **Designated States** (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH,

[Continued on next page]

(54) **Title:** NASAL DELIVERY DEVICES

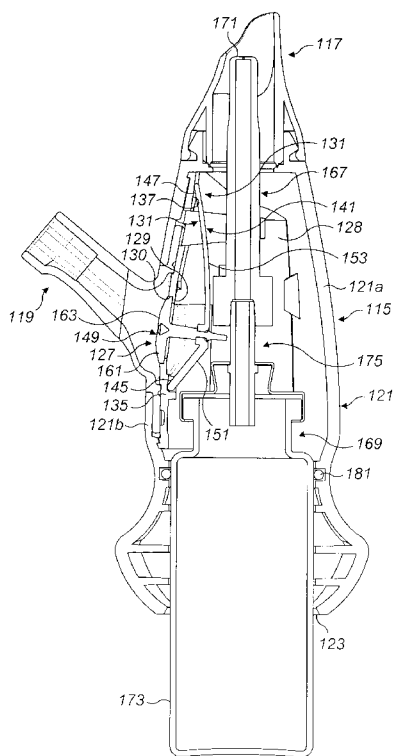


FIG. 3

(57) **Abstract:** A nasal delivery device for and method of delivering substance to a nasal airway of a subject, the delivery device comprising: a nosepiece (117) for fitting to a nasal cavity of a subject; a mouthpiece (119) into which the subject in use exhales; a delivery unit, which comprises an actuation part which is manually displaceable to actuate the delivery unit to deliver substance from the nosepiece; and a valve assembly (127) which is fluidly connected to the nosepiece and the mouthpiece, wherein the valve assembly comprises a body element (128) and a valve element (131) which is movably disposed to the body element between closed and open configurations by manual displacement of the actuation part of the delivery unit to provide for an air flow through the nosepiece simultaneously with delivery of substance.



GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published:**

- *with international search report (Art. 21(3))*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

**NASAL DELIVERY DEVICES**

The present invention relates to a nasal delivery device for and a method of delivering a substance, in particular one of a liquid, as a suspension or solution, or a powder, such as containing a medicament, especially systemic or topical pharmaceuticals, or a vaccine, to the nasal airway of a subject.

Referring to Figure 10, the nasal airway 1 comprises the two nasal cavities separated by the nasal septum, which airway 1 includes numerous ostia, such as the paranasal sinus ostia 3 and the tubal ostia 5, and olfactory cells, and is lined by the nasal mucosa. The nasal airway 1 can communicate with the nasopharynx 7, the oral cavity 9 and the lower airway 11, with the nasal airway 1 being in selective communication with the anterior region of the nasopharynx 7 and the oral cavity 9 by opening and closing of the oropharyngeal velum 13. The velum 13, which is often referred to as the soft palate, is illustrated in solid line in the closed position, as achieved by providing a certain positive pressure in the oral cavity 9, such as achieved on exhalation through the oral cavity 9, and in dashed line in the open position.

There are many nasal conditions which require treatment. One such condition is nasal inflammation, specifically rhinitis, which can be allergic or non-allergic and is often associated with infection and prevents normal nasal function. By way of example, allergic and non-allergic inflammation of the nasal airway can typically effect between 10 and 20 % of the population, with nasal congestion of the erectile tissues of the nasal concha, lacrimation, secretion of watery mucus, sneezing and itching being the most common symptoms. As will be understood, nasal congestion impedes nasal breathing and promotes oral breathing, leading to snoring and sleep disturbance. Other nasal conditions include nasal polyps which arise from the paranasal sinuses, hypertrophic adenoids, secretory otitis media, sinus disease and reduced olfaction.

In the treatment of certain nasal conditions, the topical administration of medicaments is preferable, particularly where the nasal mucosa is the prime pathological pathway, such as in treating or relieving nasal congestion. Medicaments that are commonly topically delivered include decongestants, anti-histamines, cromoglycates, steroids and antibiotics. At present, among the known anti-inflammatory pharmaceuticals, topical steroids have been shown to have an effect on nasal congestion. Topical decongestants have also been suggested for use in relieving nasal congestion. The treatment of hypertrophic adenoids and chronic secretory otitis media using topical decongestants, steroids and anti-microbial agents, although somewhat controversial, has also been proposed. Further, the topical administration of pharmaceuticals has been used to treat or at least relieve symptoms of inflammation in the anterior region of the nasopharynx, the paranasal sinuses and the auditory tubes.

Medicaments can also be systemically delivered through the nasal pathway, the nasal pathway offering a good administration route for the systemic delivery of pharmaceuticals, such as hormones, for example, oxytocin and calcitonin, and analgetics, such as anti-migraine compositions, as the high blood flow and large surface area of the nasal mucosa advantageously provides for rapid systemic uptake.

Nasal delivery is also expected to be advantageous for the administration of medicaments requiring a rapid onset of action, for example, analgetics, anti-emetics, insulin, anti-epileptics, sedatives and hypnotics, and also other pharmaceuticals, for example, cardio-vascular drugs. It is envisaged that nasal administration will provide for a fast onset of action, at a rate similar to that of injection and at a rate much faster than that of oral administration. Indeed, for the treatment of many acute conditions, nasal administration is advantageous over oral administration, since gastric stasis can further slow the onset of action following oral administration.

It is also expected that nasal delivery could provide an effective delivery route for the administration of proteins and peptides as produced by modern biotechnological techniques. For such substances, the metabolism in the intestines and the first-pass-effect in the liver represent significant obstacles for reliable and cost-efficient delivery.

Furthermore, it is expected that nasal delivery using the nasal delivery technique of the present invention will prove effective in the treatment of many common neurological diseases, such as Alzheimer's, Parkinson's, psychiatric diseases and intracerebral infections, where not possible using existing techniques. The nasal delivery technique of the present invention allows for delivery to the olfactory region, which region is located in the superior region of the nasal cavities and represents the only region where it is possible to circumvent the blood-to-brain barrier (BBB) and enable communication with the cerebrospinal fluid (CSF) and the brain.

Also, it is expected that the nasal delivery technique of the present invention will allow for the effective delivery of vaccines.

Aside from the delivery of medicaments, the irrigation of the nasal mucosa with liquids, in particular saline solutions, is commonly practised to remove particles and secretions, as well as to improve the mucociliary activity of the nasal mucosa. These solutions can be used in combination with active pharmaceuticals.

For any kind of drug delivery, accurate and reliable dosing is essential, but it is of particular importance in relation to the administration of potent drugs which have a narrow therapeutic window, drugs with potentially serious adverse effects and drugs for the treatment of serious and life-threatening conditions. For some conditions, it is essential to individualize the dosage to the particular situation, for example, in the case of diabetes mellitus. For diabetes, and, indeed, for many other conditions, the dosage of the pharmaceutical is preferably based on actual real-time measurements.

Currently, blood samples are most frequently used, but the analysis of molecules in the exhalation breath of subjects has been proposed as an alternative to blood analysis for several conditions. Breath analysis is currently used for the diagnosis of conditions such as helicobacter pylori infections which cause gastric ulcers.

WO-A-2000/051672 discloses a delivery device for delivering a substance, in particular a medicament, in a bi-directional flow through the nasal cavities, that is, an air flow which passes into one nostril, around the posterior margin of the nasal septum and in the opposite direction out of the other nostril. This bi-directional air flow advantageously acts to stimulate the sensory nerves in the nasal mucosa, thereby conditioning the subject for the delivery and providing a more comfortable delivery situation.

It is an aim of the present invention to provide nasal delivery devices and methods for delivering substances to a nasal cavity of subject, and in particular relatively-simple mechanically-actuatable delivery devices.

In one aspect the present invention provides a nasal delivery device for delivering substance to a nasal airway of a subject, comprising: a nosepiece for fitting to a nasal cavity of a subject; a mouthpiece into which the subject in use exhales; a delivery unit, which comprises an actuation part which is manually displaceable to actuate the delivery unit to deliver substance from the nosepiece; and a valve assembly which is fluidly connected to the nosepiece and the mouthpiece, wherein the valve assembly comprises a body element and a valve element which is movably disposed to the body element between closed and open configurations by manual displacement of the actuation part of the delivery unit to provide for an air flow through the nosepiece simultaneously with delivery of substance.

In another aspect the present invention provides a method of delivering substance to a nasal airway of a subject, comprising the steps of: fitting a nosepiece to a nasal cavity of a subject; the subject exhaling into a

- 5 -

mouthpiece; providing a delivery device which comprises: a delivery unit, which comprises an actuation part which is manually displaceable to actuate the delivery unit to deliver substance from the nosepiece; and a valve assembly which is fluidly connected to the nosepiece and the mouthpiece, wherein the valve assembly comprises a body element and a valve element which is movably disposed to the body element between closed and open configurations by manual displacement of the actuation part of the delivery unit; and manually displacing the actuation part of the delivery unit to move the valve element of the valve assembly relative to the body element of the valve assembly between closed and open configurations and provide an air flow through the nosepiece simultaneously with delivery of substance.

Preferred embodiments of the present invention will now be described hereinbelow by way of example only with reference to the accompanying drawings, in which:

Figures 1(a) and (b) illustrate a perspective view of a nasal delivery device in accordance with a first embodiment of the present invention;

Figure 2 illustrates an exploded perspective view of the delivery device of Figure 1;

Figure 3 illustrates a vertical sectional view of the delivery device of Figure 1, in the at rest, non-actuated configuration;

Figure 4 illustrates a vertical sectional view of the delivery device of Figure 1, in the actuated configuration;

Figure 5 illustrates an exploded, fragmentary vertical sectional view of the delivery device of Figure 1, in the actuated configuration;

Figures 6(a) to (c) illustrate the opening of the sealing member of the valve assembly by operation of the delivery unit of the delivery device of Figure 1;

Figure 7 illustrates plots of the flow rates at the nosepiece and the mouthpiece and the pressure at the mouthpiece for one exemplary device;

Figures 8(a) and (b) illustrate fragmentary vertical sectional views in the at rest, non-actuated and actuated configurations of a nasal delivery device in accordance with a second embodiment of the present invention;

Figures 9(a) and (b) illustrate fragmentary vertical sectional views in the at rest, non-actuated and actuated configurations of a nasal delivery device in accordance with a third embodiment of the present invention; and

Figure 10 schematically illustrates the anatomy of the upper respiratory tract of a human subject.

Figures 1 to 7 illustrate a manually-actuated nasal delivery device in accordance with a first embodiment of the present invention.

The delivery device comprises a housing 115, a nosepiece 117 for fitting in a nasal cavity of a subject, a mouthpiece 119 into which the subject in use exhales, such as to enable delivery of an air flow into and through the nasal airway of the subject on exhalation by the subject through the mouthpiece 119, and a delivery unit 120, which is manually actuatable to deliver substance to the nasal cavity of the subject.

The housing 115 comprises a body member 121, in this embodiment of substantially elongate, tubular section which includes an aperture 123 at one end thereof, through which projects an actuating part of the delivery unit 120, in this embodiment as defined by the base of a substance-containing chamber 173 of a substance-supply unit 169.

In this embodiment the body member 121 comprises two body sections 121a, b which are fixed together.



In this embodiment the body sections 121a, b include inter-engaging lugs 124 and detents 125, here of snap-fit type, and sealing elements 126, which act to close the air flow paths at the junctions of the body sections 121a, b.

In this embodiment the sealing elements 126 are adhesively bonded, but could alternatively be mechanically bonded, such as by welding.

In an alternative embodiment the sealing elements 126 could be omitted.

The housing 115 further comprises a valve assembly 127 which is fluidly connected to the nosepiece 117 and the mouthpiece 119, and operable between closed and open configurations, as illustrated in Figures 3 and 4, such as to provide for an air flow, in this embodiment in the form of a burst of air, through the nosepiece 117 simultaneously with actuation of the delivery unit 120, as will be described in more detail hereinbelow.

The valve assembly 127 comprises a main, body element 128 which includes a valve seat 129 defining a valve opening 130, and a valve element 131 which is movably disposed to the body element 128 between closed and open positions, as illustrated in Figures 3 and 4.

As particularly illustrated in Figure 3, the body element 128 comprises a pivot 135, in this embodiment to one, lower side of the valve seat 129, to which one end 145 of the valve element 131 is pivoted, and a sliding surface 137, in this embodiment to the other, upper side of the valve seat 129, against which the other end 147 of the valve element 131 is slideable.

The valve element 131 comprises an elongate arm 141, in this embodiment a flexible arm, one end 145, in this embodiment the lower end, of which is pivoted to the pivot 135 of the body element 128, and the other, upper end 147 of which slideably engages the sliding surface 137 of the body element 128, and a valve member 149 which is supported by the arm 141.

In this embodiment the arm 141 comprises a first, here lower, arm section 151, which is biased, here inwardly, such that, when the valve element 131 is in the closed, rest position, the lower arm section 151 is inclined inwardly relative to the longitudinal axis of the housing 115 and engageable by the substance-supply unit 169 when manually actuated to move the valve element 131 to the open position, as will be described in more detail hereinbelow.

In this embodiment the arm 141 further comprises a second, here upper, arm section 153, which engages the sliding surface 137 of the body element 128 and acts to bias the valve element 131 to the closed position.

In this embodiment the valve member 149 comprises a seal 161, in this embodiment a flexible or resilient element, which acts to close the valve opening 130 as defined by the valve seat 129 when the valve element 131 is in the closed position, and a support 163 which supports a central region of the seal 161.

With this configuration, and referring to Figures 6(a) to (c), where the seal 161 is centrally supported, when the valve element 131 is moved to the open position, the support 163 biases the central region of the seal 161, as illustrated in Figure 6(b), causing the seal 161 to bulge outwardly in this central region and thus provide that the seal 161 engages the valve seat 129 only at the peripheral edge of the seal 161, until the point is reached when the seal 161 is suddenly and explosively released from the valve seat 129, as illustrated in Figure 6(c).

This mode of release is believed to be particularly effective in the present application where it is desired to achieve a sudden, initial burst of air flow, in that substantially the entire sealing surface of the seal 161 is released in one instant, which compares to an alternative mode of a peeling-type release, where a smaller section of a sealing surface is released, followed by

the remainder of the sealing surface, which tends to provide a smaller initial burst pressure.

In this embodiment the delivery unit 120 comprises an outlet unit 167 for delivering substance into the nasal airway of the subject, and a substance-supply unit 169 for delivering substance to the outlet unit 167.

In this embodiment the valve assembly 127 provides for a pre-actuation efficiency of less than 5 L/min when a user is developing an exhalation pressure of 3 kPa, preferably less than 5 L/min when a user is developing an exhalation pressure of 10 kPa, more preferably less than 1 L/min when a user is developing an exhalation pressure of 3 kPa, still more preferably less than 1 L/min when a user is developing an exhalation pressure of 10 kPa, yet more preferably substantially no flow when a user is developing an exhalation pressure of 3 kPa, and still yet more preferably substantially no flow when a user is developing an exhalation pressure of 10 kPa; the pre-actuation efficiency being a measure of the volume of air which escapes from the device prior to actuation as a fraction of the volume of air delivered into the mouthpiece 119.

In this embodiment the delivery device is configured to provide a post-actuation efficiency of at least 80% at a flow rate of 50 L/min and an exhalation pressure of 3 kPa, preferably at least 85% at a flow rate of 50 L/min and an exhalation pressure of 3 kPa, more preferably at least 88% at a flow rate of 50 L/min and an exhalation pressure of 3 kPa, and yet more preferably at least 90% at a flow rate of 50 L/min and an exhalation pressure of 3 kPa; the post-actuation efficiency being a measure of the volume of air delivered from the nosepiece 117 as a fraction of the volume of air delivered into the mouthpiece 119.

Figure 7 illustrates, for one exemplary device, plots of the flow rates at the nosepiece 117 and the mouthpiece 119 and the pressure at the mouthpiece 119.

In this embodiment the pre-actuation efficiency of 1 L/min at a pre-actuation pressure of 5 kPa.

In this embodiment the post-actuation efficiency is 88% at a flow rate of 57.1 L/min.

In this embodiment, the valve element 131 provides for a burst of air flow on opening thereof, having a first, initial burst phase followed by a second, extended burst phase, wherein the peak flow rate in the initial burst phase has a higher flow rate than the average flow rate in the extended burst phase, and the extended burst phase is of substantially greater duration than the initial burst phase.

In this embodiment the peak flow rate in the initial burst phase is at least 10%, preferably at least 15%, and more preferably at least 20%, greater than that of the average flow rate of the extended burst phase in a period corresponding to ten times the duration of the period in which substance is delivered from the nosepiece 117 by the delivery unit 120.

In this embodiment the delivery unit 120 provides a spray which commences 54 ms after opening of the sealing member 149 and terminates 134 ms after opening of the sealing member 149.

In one embodiment the delivery unit 120 provides for delivery of substance subsequent to opening of the sealing member 149.

In one embodiment the delivery unit 120 provides for delivery of substance in a period less than about 250 ms from opening of the sealing member 149, preferably less than about 200 ms from opening of the sealing member 149, more preferably less than about 150 ms from opening of the sealing member 149, and still more preferably more preferably less than about 100 ms from opening of the sealing member 149.

In one embodiment the delivery unit 120 provides for delivery of substance commencing less than about 150 ms subsequent to opening of the sealing member 149, preferably less than about 100 ms subsequent to opening of the sealing member 149, still more preferably less than about 50 ms subsequent to opening of the sealing member 149, yet more preferably less than more than about 25 ms subsequent to opening of the sealing member 149, still more preferably less than about 15 ms subsequent to opening of the sealing member 149.

In this embodiment the outlet unit 167 comprises a nozzle 171 for delivering substance to the nasal airway of the subject. In this embodiment the nozzle 171 is configured to provide an aerosol spray. In an alternative embodiment, for the delivery of a liquid, the nozzle 171 could be configured to deliver a liquid jet as a column of liquid.

In a preferred embodiment the distal end of the outlet unit 167 is configured to extend at least about 2 cm, preferably at least about 3 cm, and more preferably from about 2 cm to about 3 cm, into the nasal cavity of the subject.

In this embodiment the substance supply unit 169 is a pump unit, which comprises a substance-containing chamber 173 which contains substance and extends from the aperture 123 in the housing 115 as the actuating part of the substance-supply unit 169, and a mechanical delivery pump 175 which is actuatable, here by depression of the substance-containing chamber 173, typically by a finger or thumb of the subject, to deliver a metered dose of substance from the substance-containing chamber 173 to the outlet unit 167 and from the nozzle 171 thereof, here as an aerosol spray.

In this embodiment the substance-containing chamber 173, when depressed to actuate the substance supply unit 169, engages the lower arm section

151 of the arm 141 of the valve element 131, such as simultaneously to provide for actuation of the substance-supply unit 169 and opening of the seal 161 of the valve element 131, whereby substance, here in the form of a spray, and an air flow, here as a burst of air, are simultaneously delivered to the nasal cavity of the subject.

In this embodiment the mechanical delivery pump 175 is a liquid delivery pump for delivering a metered dose of substance, but in an alternative embodiment the mechanical delivery pump 175 could be a powder delivery pump, which delivers metered doses of a powdered substance on actuation thereof.

In this embodiment the substance-supply unit 169 is a multi-dose unit for delivering a plurality of metered doses of substance in successive delivery operations.

In an alternative embodiment the substance-supply unit 169 could be a single-dose unit for delivering a single metered dose of substance or a duo-dose unit for delivering two metered doses of substance in two successive delivery operations.

In another alternative embodiment the substance-supply unit 169 could comprise a dry powder delivery unit which delivers metered doses of a substance, as a dry powder, on actuation thereof.

In yet another alternative embodiment the substance-supply unit 169 could comprise a nebulizer which delivers metered doses of a substance, as an aerosol spray, on actuation thereof.

In still another alternative embodiment the substance-supply unit 169 could comprise an aerosol canister for delivering metered volumes of a propellant, preferably a hydrofluoroalkane (HFA) propellant or the like, containing substance, either as a suspension or solution.

In this embodiment the housing 115 further comprises a sealing member 181, here an annular seal, in the form of an O-ring, which slideably receives the substance-containing chamber 173 of the substance-supply unit 169, such as to prevent the escape of the delivered air flow from the aperture 123 in the housing 115.

In one embodiment the sealing member 181 could be omitted.

Figures 8(a) and (b) illustrate a nasal delivery device in accordance with a second embodiment of the present invention.

The delivery device of this embodiment is substantially the same as the delivery device of the first-described embodiment, and thus, in order to avoid unnecessary duplication of description, only the differences will be described in detail, with like parts being designated by like reference signs.

The delivery device of this embodiment differs from that of the first-described embodiment principally in that the valve member 149 is configured such that the support 163 extends across substantially the entire width of the valve opening 130. In this way, the seal 161 is not able to bulge in the manner of the above-described embodiment, and is instead opened by a peeling action. Figure 8(a) illustrates the valve assembly 127 in the at rest, non-actuated configuration. Figure 8(b) illustrates the valve assembly 127 in the actuated configuration.

Figures 9(a) and (b) illustrate a nasal delivery device in accordance with a third embodiment of the present invention.

The delivery device of this embodiment is very similar to the delivery device of the first-described embodiment, and thus, in order to avoid unnecessary duplication of description, only the differences will be described in detail, with like parts being designated by like reference signs.

The delivery device of this embodiment differs from that of the first-described embodiment principally in that the seal 161 is not supported by the arm 141, but is instead a separate element, which is displaced by movement of the arm 141, as caused by manual actuation of the substance-supply unit 169. Figure 9(a) illustrates the valve assembly 127 in the at rest, non-actuated configuration. Figure 9(b) illustrates the valve assembly 127 in the actuated configuration.

In this embodiment the seal 161 comprises a flexible element, here in the form of a flap, and in one embodiment a resilient element, which is engaged by an engagement element 185 on the arm 141.

In this embodiment the engagement element 185 comprises a projection which acts to cause the seal 161 to bulge in the manner of the first-described embodiment.

In an alternative embodiment the engagement element 185 could extend across substantially the width of the valve opening 130, causing the seal 161 to be moved from the valve seat 129 with a peeling action in a similar manner to the second-described embodiment.

Finally, it will be understood that the present invention has been described in its preferred embodiments and can be modified in many different ways without departing from the scope of the invention as defined by the appended claims.



**CLAIMS**

1. A nasal delivery device for delivering substance to a nasal airway of a subject, comprising:  
a nosepiece for fitting to a nasal cavity of a subject;  
a mouthpiece into which the subject in use exhales;  
a delivery unit, which comprises an actuation part which is manually displaceable to actuate the delivery unit to deliver substance from the nosepiece; and  
a valve assembly which is fluidly connected to the nosepiece and the mouthpiece, wherein the valve assembly comprises a body element and a valve element which is movably disposed to the body element between closed and open configurations by manual displacement of the actuation part of the delivery unit to provide for an air flow through the nosepiece simultaneously with delivery of substance.
2. The delivery device of claim 1, wherein the body element includes a pivot, and the valve element comprises an arm, one end of which is pivoted to the pivot of the body element between the closed and open configurations.
3. The delivery device of claim 2, wherein the arm is at least in part resilient.
4. The delivery device of claim 2 or 3, wherein the body element includes a sliding surface, against which the other end of the arm is slideable.
5. The delivery device of any of claims 2 to 4, wherein the arm comprises a first arm section which is configured such that, when the valve element is in the closed configuration, the lower arm section is engageable by displacement of the actuation part of the delivery unit.

- 16 -

6. The delivery device of claim 5, wherein the arm is biased inwardly relative to the longitudinal axis of delivery device.
7. The delivery device of claim 5 or 6, wherein the arm is inclined inwardly relative to the longitudinal axis of the delivery device when the valve element is in the closed configuration.
8. The delivery device of any of claims 5 to 7, wherein the first arm section comprises a substantially rigid section.
9. The delivery device of any of claims 5 to 8, wherein the arm comprises a second arm section which engages the sliding surface of the body element.
10. The delivery device of claim 9, wherein the first and second arm sections enclose an obtuse angle.
11. The delivery device of claim 9 or 10, wherein the second arm section is a resilient section which acts to bias the valve element to the closed configuration.
12. The delivery device of any of claims 1 to 11, wherein the body element includes a valve seat which defines a valve opening, and the valve element comprises a seal which acts to close the valve opening when the valve element is in the closed position.
13. The delivery device of claim 12, wherein the seal comprises a resilient element.
14. The delivery device of claim 12 or 13, wherein the valve element comprises a support which supports a central region of the seal, such as to allow a peripheral region of the seal to engage the valve seat

- 17 -

and the central region to be deflected relative to the peripheral region, thereby allowing for sudden release of the seal.

15. The delivery device of claim 12 or 13, wherein the valve element comprises a support which extends substantially across a width of the valve opening.
16. The delivery device of claim 12 or 13, wherein the seal is separate to and not supported by the arm, and displaced by movement of the arm.
17. The delivery device of claim 16, wherein the seal comprises a resilient element, and the arm comprises an engagement element which engages the seal with movement of the arm.
18. The delivery device of claim 17, wherein the seal comprises a resilient flap.
19. The delivery device of any of claims 1 to 18, wherein the valve assembly, on opening of the valve element, provides for a burst of air flow, having a first, initial burst phase followed by a second, extended burst phase, wherein the peak flow rate in the first burst phase has a higher flow rate than the average flow rate in the second burst phase, and the second burst phase is of substantially greater duration than the first burst phase.
20. The delivery device of claim 19, wherein the peak flow rate in the first burst phase is at least 10% greater than that of the average flow rate of the second burst phase in a period corresponding to ten times the duration of the period in which substance is delivered from the delivery unit.

21. The delivery device of claim 20, wherein the peak flow rate in the first burst phase is at least 15% greater than that of the average flow rate of the second burst phase in a period corresponding to ten times the duration of the period in which substance is delivered from the delivery unit.
22. The delivery device of claim 21, wherein the peak flow rate in the first burst phase is at least 20% greater than that of the average flow rate of the second burst phase in a period corresponding to ten times the duration of the period in which substance is delivered from the delivery unit.
23. The delivery device of any of claims 1 to 22, further comprising:  
a housing which includes an aperture through which the actuation part of the delivery unit extends.
24. The delivery device of claim 23, wherein the housing further comprises a sealing member which slideably receives the actuation part to prevent air flow from the aperture in the housing.
25. The delivery device of any of claims 1 to 24, wherein the valve assembly provides for a pre-actuation efficiency of less than 5 L/min when a user is developing an exhalation pressure of 3 kPa.
26. The delivery device of claim 25, wherein the valve assembly provides for a pre-actuation efficiency of less than 5 L/min when a user is developing an exhalation pressure of 10 kPa.
27. The delivery device of claim 25, wherein the valve assembly provides for a pre-actuation efficiency of less than 1 L/min when a user is developing an exhalation pressure of 3 kPa.

28. The delivery device of claim 25, wherein the valve assembly provides for a pre-actuation efficiency of less than 1 L/min when a user is developing an exhalation pressure of 10 kPa.
29. The delivery device of claim 25, wherein the valve assembly provides for a pre-actuation efficiency of 0 L/min when a user is developing an exhalation pressure of 3 kPa.
30. The delivery device of claim 25, wherein the valve assembly provides for a pre-actuation efficiency of 0 L/min when a user is developing an exhalation pressure of 10 kPa.
31. The delivery device of any of claims 1 to 30, wherein the delivery device is configured to provide at least 80% of the air as delivered into the mouthpiece to the nosepiece when delivered at a flow rate of 50 L/min and an exhalation pressure of 3 kPa.
32. The delivery device of claim 31, wherein the delivery device is configured to provide at least 88% of the air as delivered into the mouthpiece to the nosepiece when delivered at a flow rate of 50 L/min and an exhalation pressure of 3 kPa.
33. The delivery device of claim 32, wherein the delivery device is configured to provide at least 90% of the air as delivered into the mouthpiece to the nosepiece when delivered at a flow rate of 50 L/min and an exhalation pressure of 3 kPa.
34. The delivery device of any of claims 1 to 33, wherein the delivery unit provides for delivery of substance subsequent to opening of the valve element.

- 20 -

35. The delivery device of claim 34, wherein the delivery unit provides for delivery of substance in a period less than about 250 ms from opening of the sealing member.
36. The delivery device of claim 35, wherein the delivery unit provides for delivery of substance in a period less than about 200 ms from opening of the sealing member.
37. The delivery device of claim 35, wherein the delivery unit provides for delivery of substance in a period less than about 150 ms from opening of the sealing member.
38. The delivery device of claim 35, wherein the delivery unit provides for delivery of substance in a period less than about 150 ms from opening of the sealing member.
39. The delivery device of claim 35, wherein the delivery unit provides for delivery of substance in a period less than about 100 ms from opening of the sealing member.
40. The delivery device of any of claims 34 to 39, wherein the delivery unit provides for delivery of substance commencing less than about 150 ms subsequent to opening of the valve element.
41. The delivery device of claim 40, wherein the delivery unit provides for delivery of substance commencing less than about 100 ms subsequent to opening of the valve element.
42. The delivery device of claim 40, wherein the delivery unit provides for delivery of substance commencing less than about 50 ms subsequent to opening of the valve element.

43. The delivery device of claim 40, wherein the delivery unit provides for delivery of substance commencing less than about 25 ms subsequent to opening of the valve element.
44. The delivery device of claim 40, wherein the delivery unit provides for delivery of substance commencing less than about 15 ms subsequent to opening of the valve element.
45. The delivery device of any of claims 1 to 44, wherein the delivery unit comprises an outlet unit from which substance is delivered through the nosepiece and a substance-supply unit which is actuatable to deliver substance to the outlet unit.
46. The delivery device of claim 45, wherein the outlet unit comprises a spray nozzle.
47. The delivery device of claim 45 or 46, wherein the actuation part of the delivery unit comprises a substance-containing chamber of the substance-supply unit.
48. The delivery device of any of claims 1 to 47, wherein the substance-supply unit comprises a mechanical delivery pump which is actuatable by depression of the substance-containing chamber.
49. A method of delivering substance to a nasal airway of a subject, comprising the steps of:
  - fitting a nosepiece to a nasal cavity of a subject;
  - the subject exhaling into a mouthpiece;
  - providing a delivery device which comprises: a delivery unit, which comprises an actuation part which is manually displaceable to actuate the delivery unit to deliver substance from the nosepiece; and a valve assembly which is fluidly connected to the nosepiece and the mouthpiece, wherein the valve assembly comprises a body element

- 22 -

and a valve element which is movably disposed to the body element between closed and open configurations by manual displacement of the actuation part of the delivery unit; and  
manually displacing the actuation part of the delivery unit to move the valve element of the valve assembly relative to the body element of the valve assembly between closed and open configurations and provide an air flow through the nosepiece simultaneously with delivery of substance.



1 / 11

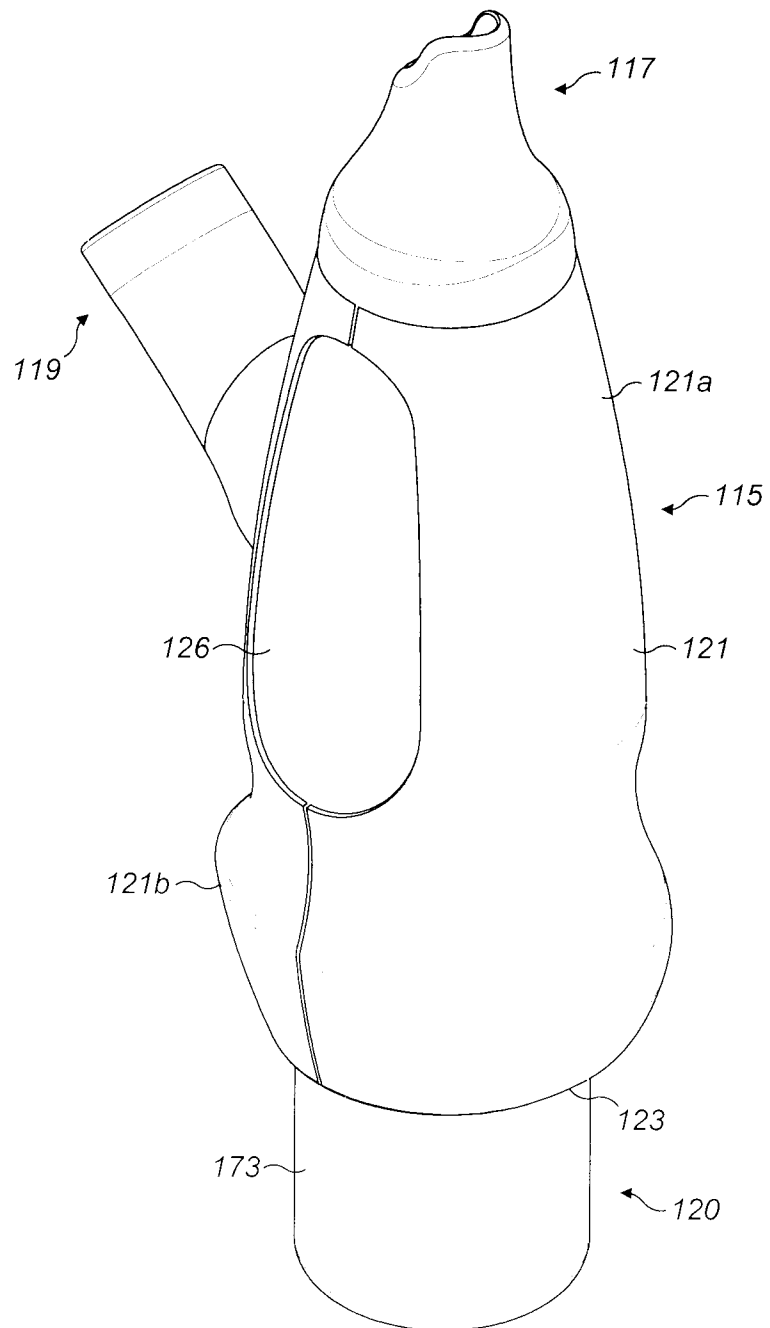


FIG. 1(a)

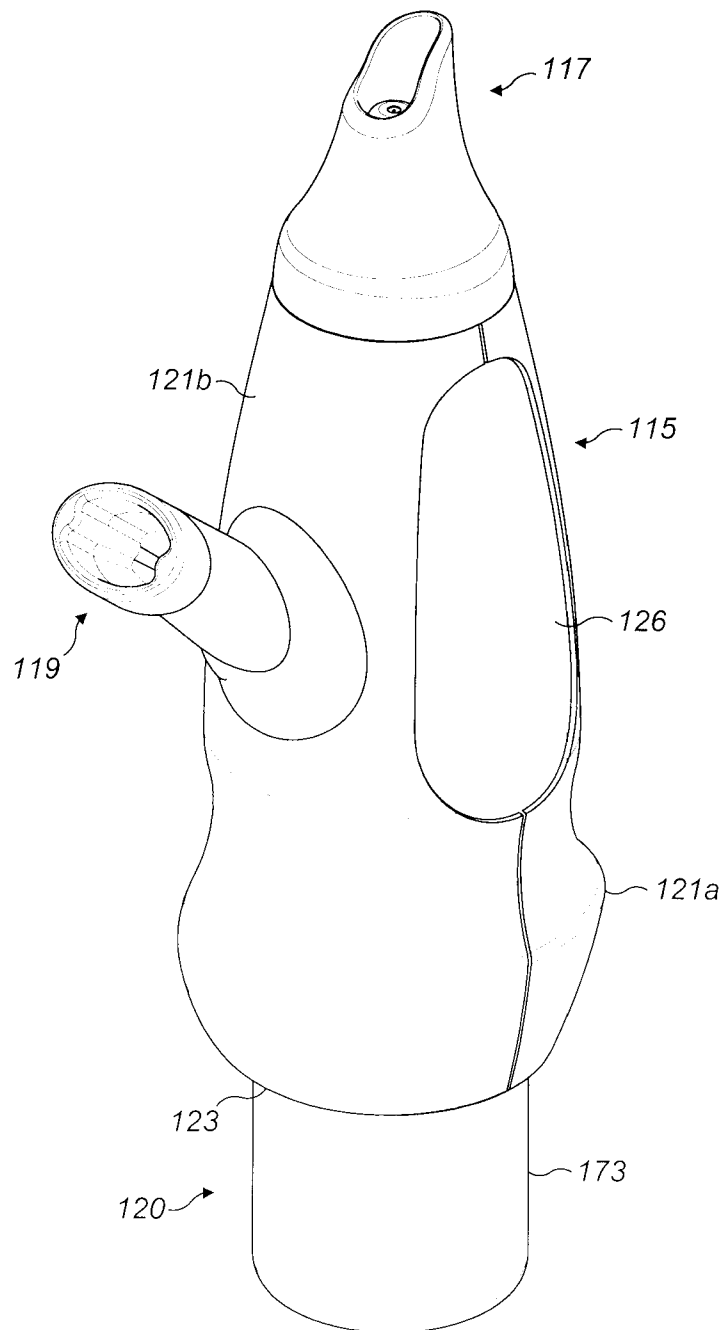


FIG. 1(b)

3 / 11

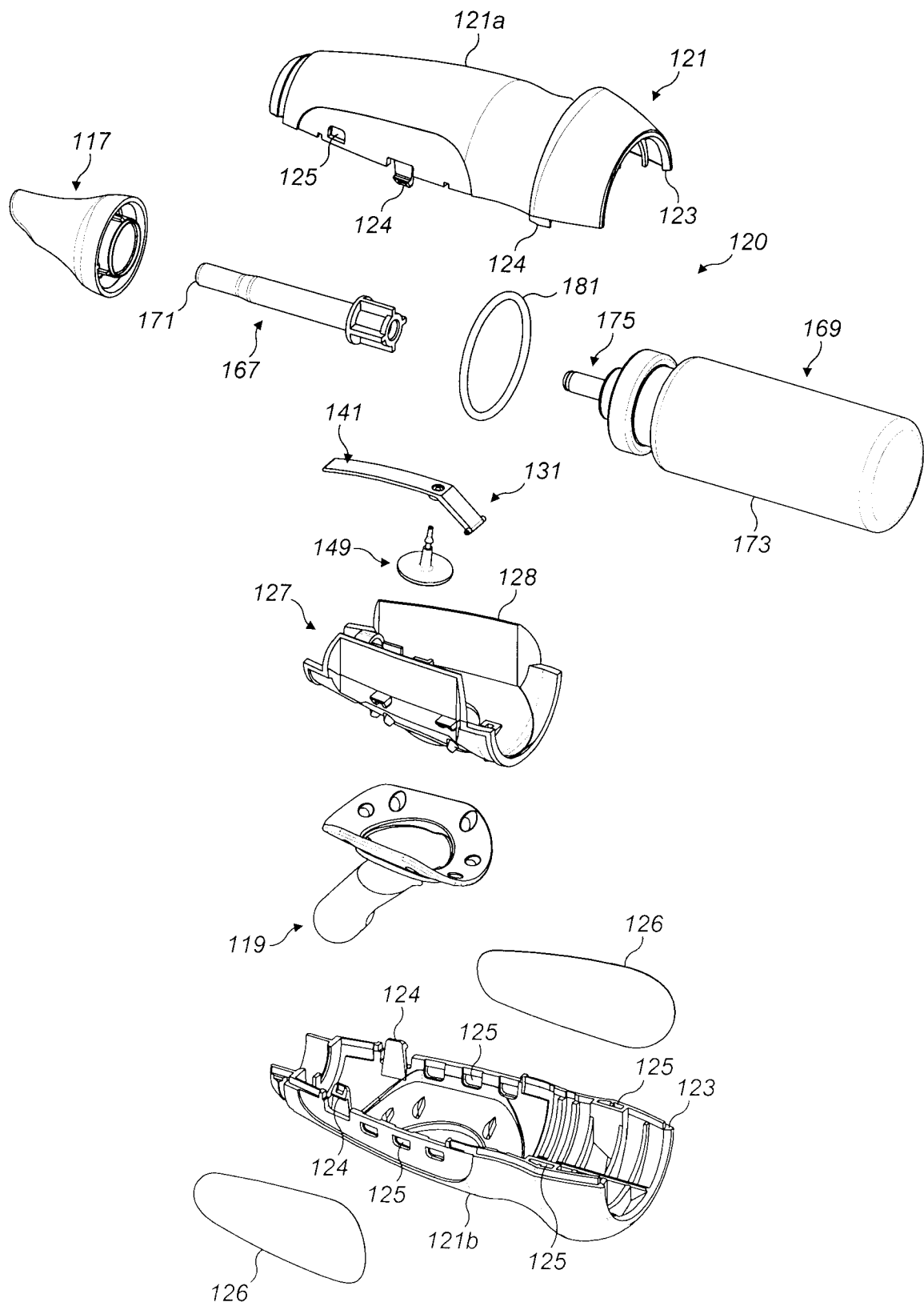


FIG. 2

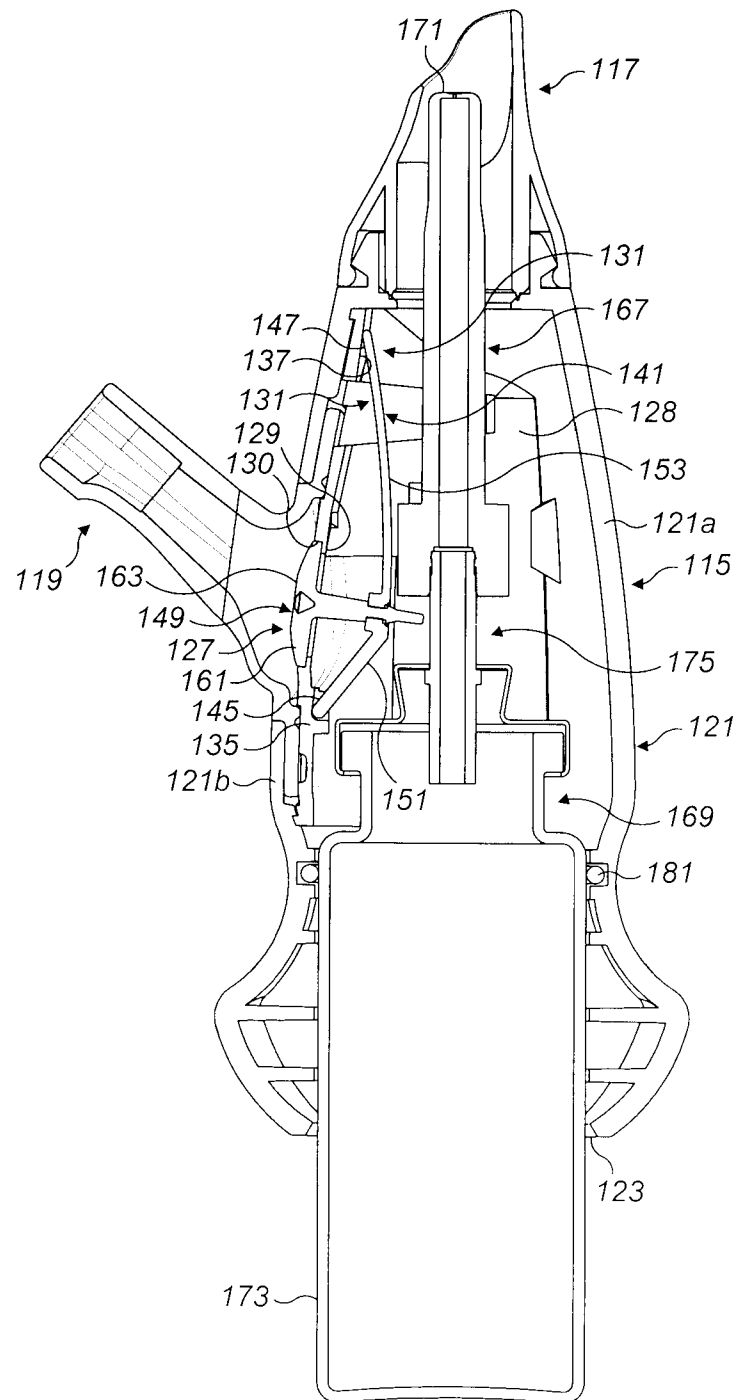


FIG. 3

5 / 11

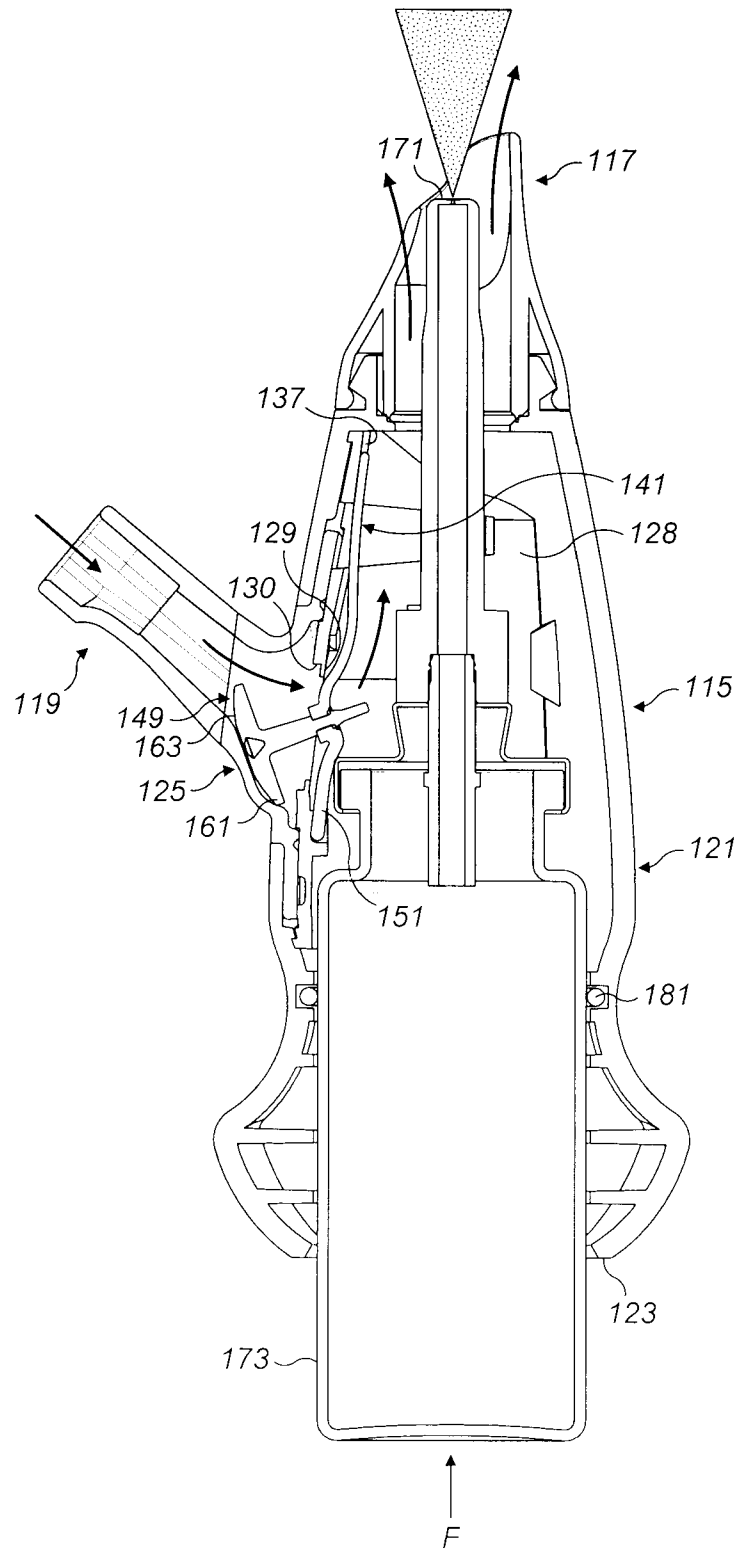
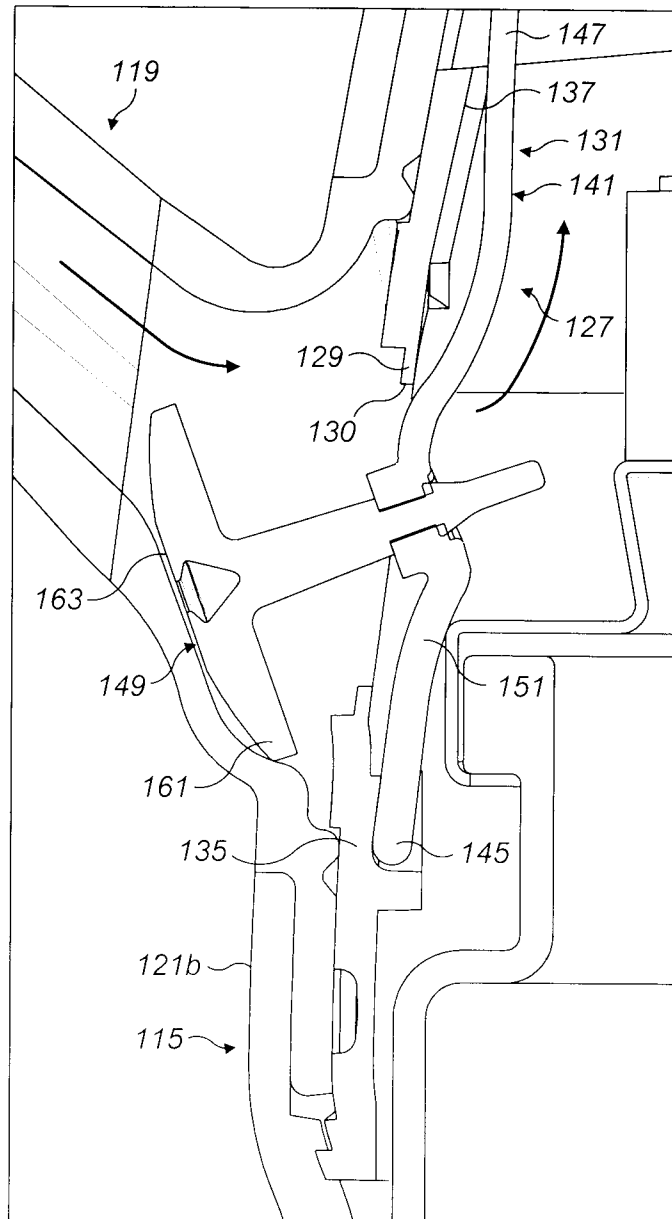


FIG. 4

**FIG. 5**

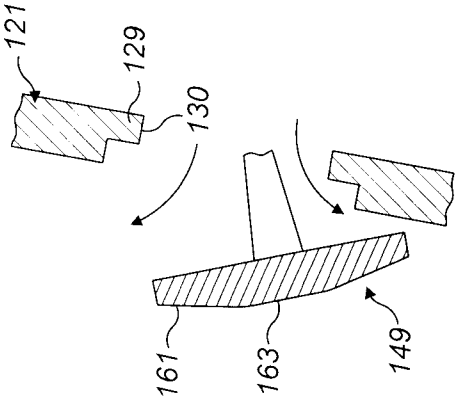


FIG. 6(c)

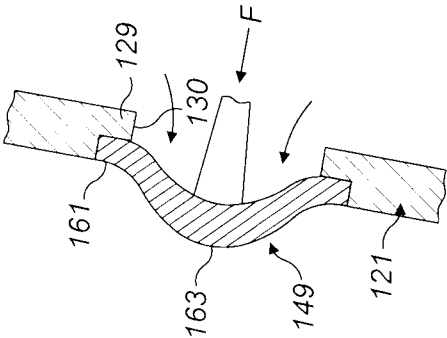


FIG. 6(b)

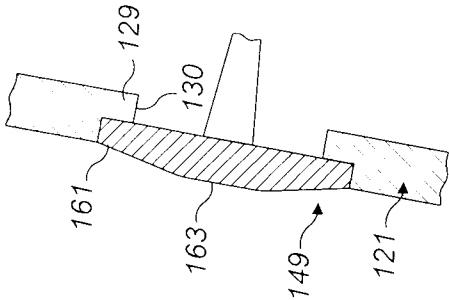


FIG. 6(a)

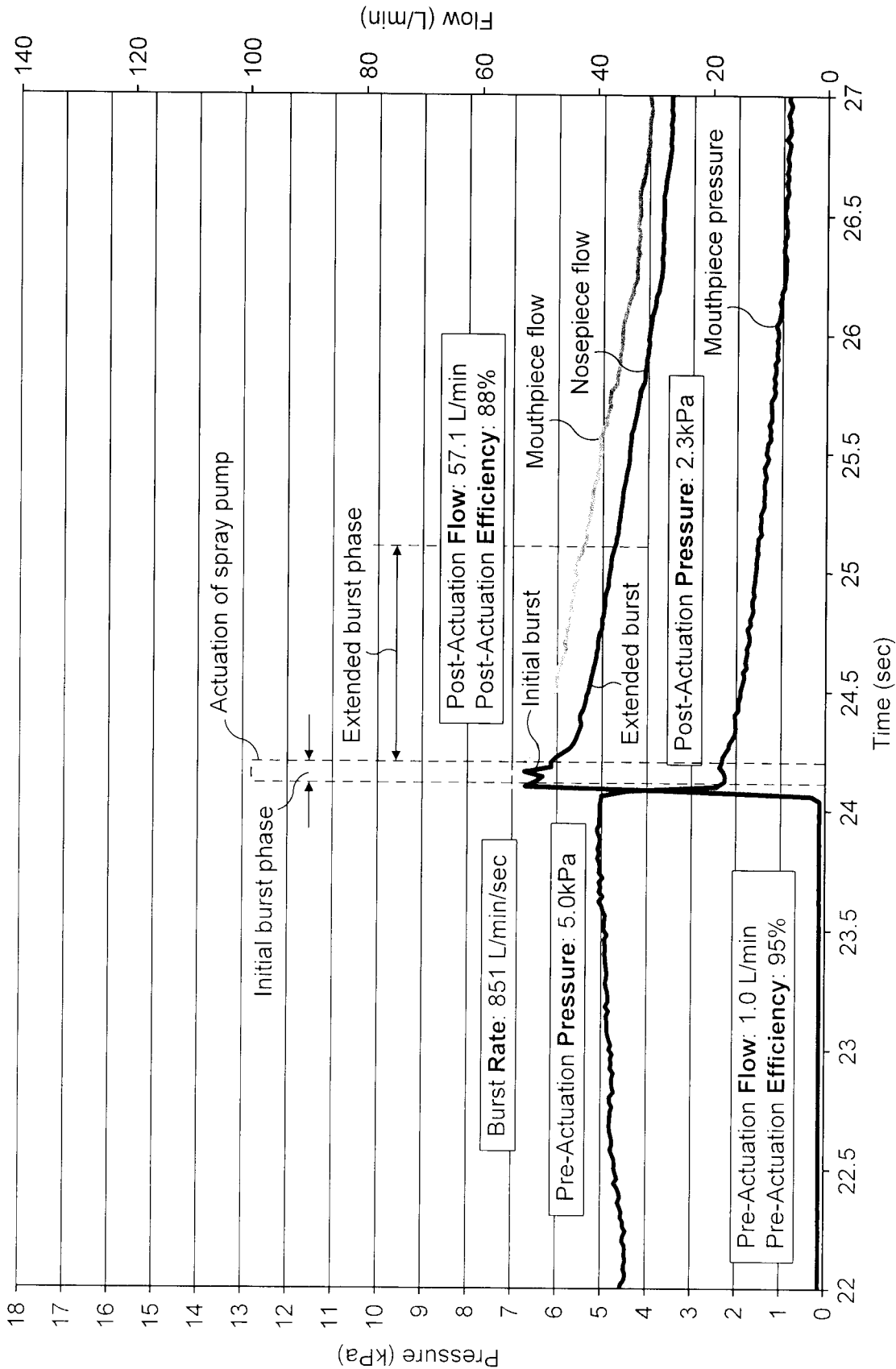


FIG. 7



9 / 11

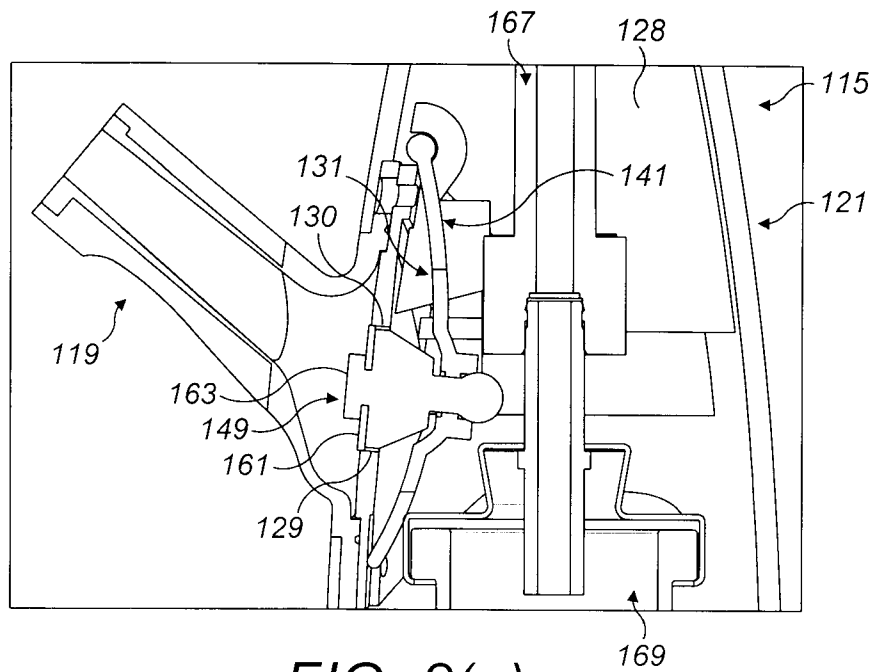


FIG. 8(a)

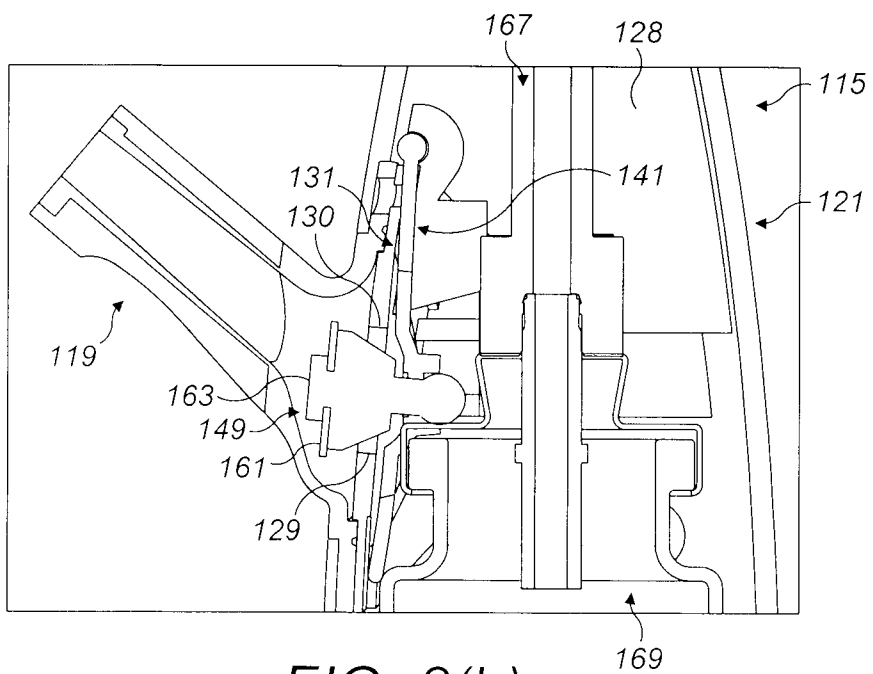
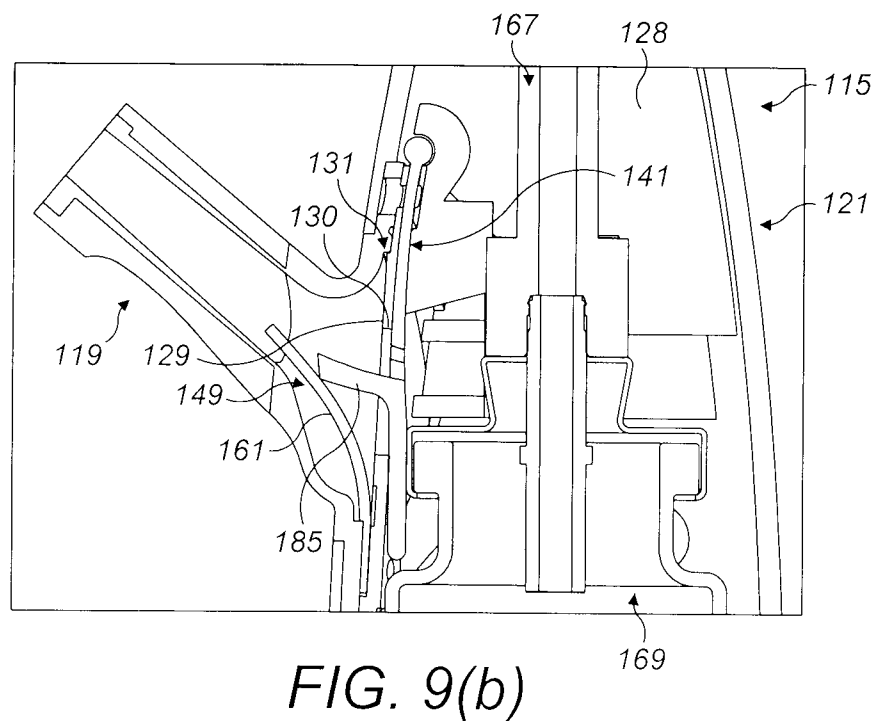
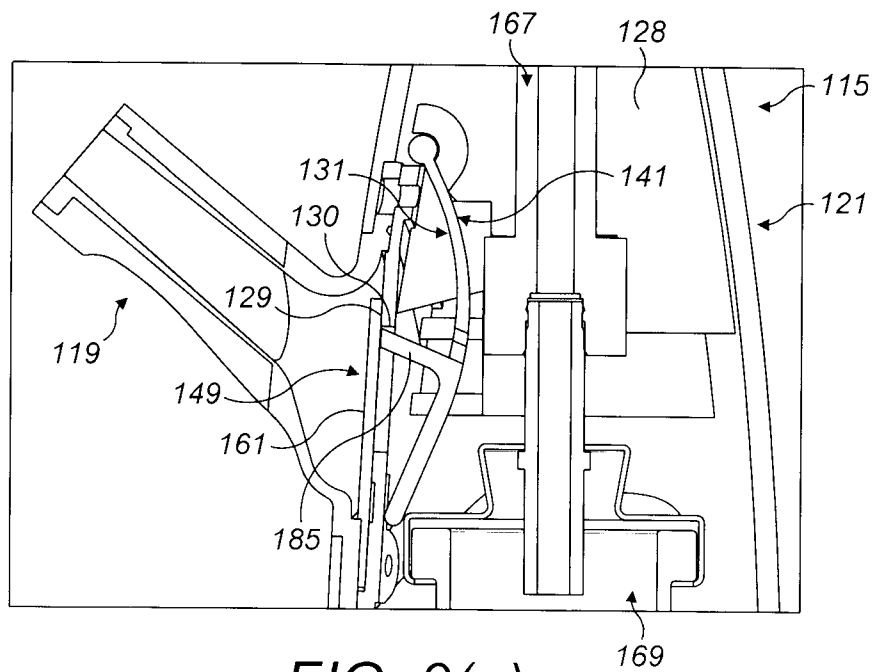


FIG. 8(b)

10 / 11



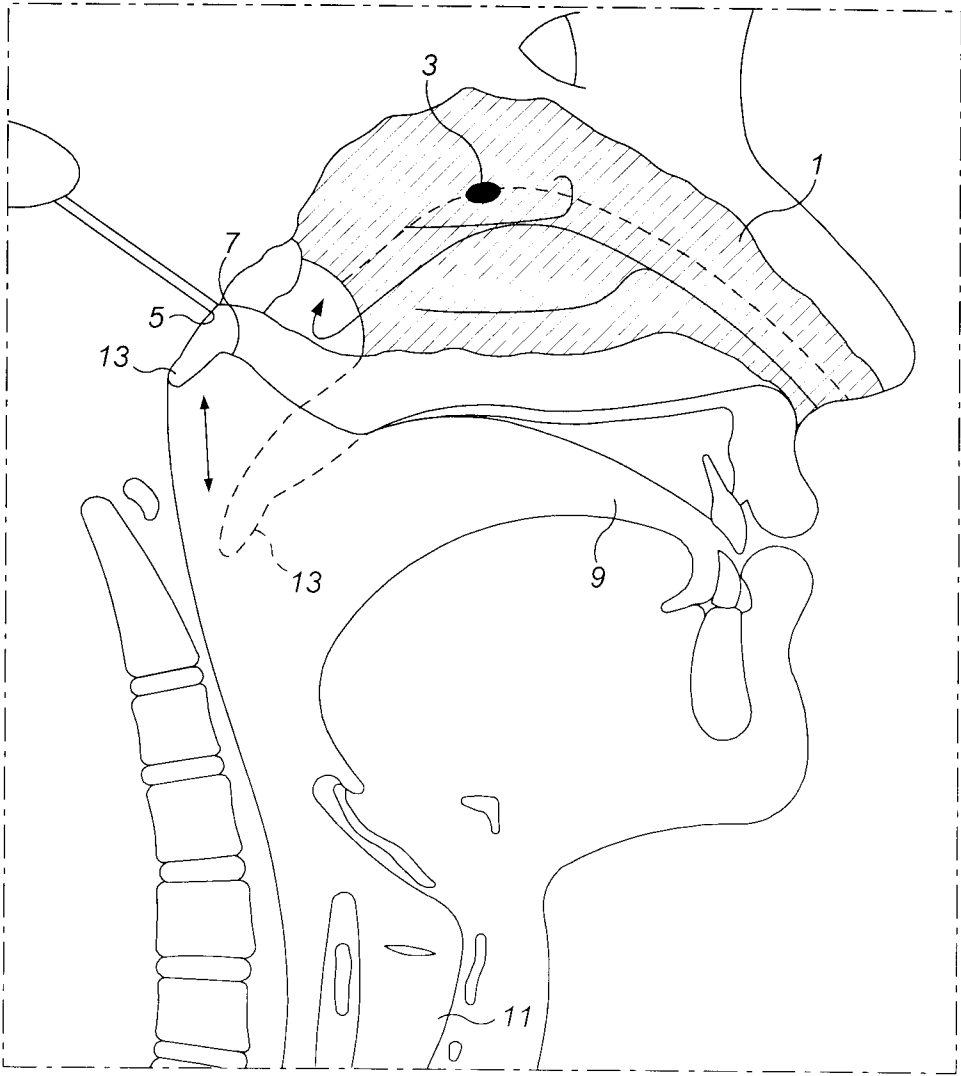


FIG. 10

## INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2013/053746

## A. CLASSIFICATION OF SUBJECT MATTER

INV. A61M15/08 A61M15/00  
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2011/088690 A1 (DJUPESLAND PER GISLE [NO] ET AL) 21 April 2011 (2011-04-21) paragraphs [0001], [0085] - [0125]; figures 2-10 paragraphs [0085] - [0262] -----	1,12,13, 19-48
X	US 6 648 848 B1 (KELDMANN ERIK [DK] ET AL) 18 November 2003 (2003-11-18)  columns 1,4,5,8, paragraph 60; figures 17-20 -----	1,12,13, 16, 18-22, 25-33, 45-47
A	WO 00/51672 A1 (DJUPESLAND PER GISLE [NO]) 8 September 2000 (2000-09-08) cited in the application pages 6-15,17-; figures 6.8,9 -----	1-47



Further documents are listed in the continuation of Box C.



See patent family annex.

## \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&amp;" document member of the same patent family

Date of the actual completion of the international search

7 June 2013

Date of mailing of the international search report

18/06/2013

Name and mailing address of the ISA/

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Authorized officer

Loughman, John

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP2013/053746

## Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 49  
because they relate to subject matter not required to be searched by this Authority, namely:  
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

Continuation of Box II.1

Claims Nos.: 49

The subject matter of claim 49 involves delivering a substance to the airways of a patient which is considered a medical method for the treatment of the human body by therapy. Such methods are excluded from search (Rule 39(iv) PCT) and preliminary examination (Rule 67(iv) PCT). Therefore no opinion is given with regard to novelty, inventive step or industrial applicability for claim 49.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2013/053746

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2011088690	A1	21-04-2011	AU 2008306635 A1 09-04-2009
			CA 2701409 A1 09-04-2009
			CN 101918061 A 15-12-2010
			EP 2197525 A1 23-06-2010
			GB 2453841 A 22-04-2009
			GB 2459266 A 21-10-2009
			JP 2010540147 A 24-12-2010
			KR 20100068478 A 23-06-2010
			RU 2010117362 A 20-11-2011
			US 2011088690 A1 21-04-2011
			WO 2009044172 A1 09-04-2009
-----			
US 6648848	B1	18-11-2003	AT 274956 T 15-09-2004
			AU 730843 B2 15-03-2001
			AU 7639298 A 30-12-1998
			BR 9809499 A 20-06-2000
			CA 2291005 A1 03-12-1998
			CN 1258223 A 28-06-2000
			CZ 9904177 A3 16-02-2000
			DE 69825995 D1 07-10-2004
			DE 69825995 T2 08-09-2005
			DK 0986413 T3 20-09-2004
			EP 0986413 A1 22-03-2000
			ES 2229496 T3 16-04-2005
			HK 1027300 A1 12-11-2004
			HU 0002538 A2 28-12-2000
			JP 2001526577 A 18-12-2001
			NO 995798 A 26-11-1999
			NZ 501157 A 27-04-2001
			PL 336975 A1 31-07-2000
			PT 986413 E 31-12-2004
			SK 160499 A3 11-07-2000
			TR 9902899 T2 22-05-2000
			US 6648848 B1 18-11-2003
			US 2002165482 A1 07-11-2002
			WO 9853869 A1 03-12-1998
-----			
WO 0051672	A1	08-09-2000	AT 285810 T 15-01-2005
			AT 487506 T 15-11-2010
			AT 514445 T 15-07-2011
			AU 766410 B2 16-10-2003
			BR 0008650 A 26-12-2001
			CA 2364009 A1 08-09-2000
			CN 1342093 A 27-03-2002
			CN 1736502 A 22-02-2006
			DE 60017099 D1 03-02-2005
			DE 60017099 T2 12-01-2006
			DK 1161274 T3 09-05-2005
			DK 1180378 T3 21-02-2011
			DK 1555038 T3 17-10-2011
			EP 1161274 A1 12-12-2001
			EP 1180378 A2 20-02-2002
			EP 1555038 A2 20-07-2005
			EP 2332603 A2 15-06-2011
			EP 2340865 A1 06-07-2011
			ES 2235836 T3 16-07-2005
			GB 2349092 A 25-10-2000
			HK 1039459 A1 13-05-2005

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2013/053746

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
	ID	30286 A	15-11-2001
	IL	144988 A	31-08-2011
	JP	4543553 B2	15-09-2010
	JP	2002537908 A	12-11-2002
	JP	2010172761 A	12-08-2010
	MX	PA01008849 A	21-07-2003
	NO	20014182 A	01-11-2001
	NZ	514442 A	29-08-2003
	PL	206121 B1	30-07-2010
	PL	350220 A1	18-11-2002
	PT	1161274 E	31-05-2005
	PT	1180378 E	14-02-2011
	SI	1161274 T1	31-08-2005
	SI	1180378 T1	29-04-2011
	TR	200102563 T2	22-04-2002
	US	6715485 B1	06-04-2004
	US	2004182388 A1	23-09-2004
	US	2006219240 A1	05-10-2006
	US	2006219241 A1	05-10-2006
	US	2006225732 A1	12-10-2006
	US	2006231094 A1	19-10-2006
	WO	0051672 A1	08-09-2000
-----			