(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 December 2018 (13.12.2018)

WIPO | PCT

(10) International Publication Number
WO 2018/226928 A1

(51) International Patent Classification:
A61M 16/00 (2006.01) *A61M 16/20* (2006.01)
A61M 16/01 (2006.01) *A61M 11/04* (2006.01)
A61M 16/10 (2006.01) *C01B 21/20* (2006.01)
A61M 16/12 (2006.01) *A61M 16/06* (2006.01)

(21) International Application Number:
PCT/US2018/036412

(22) International Filing Date:
07 June 2018 (07.06.2018)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/516,973 08 June 2017 (08.06.2017) US

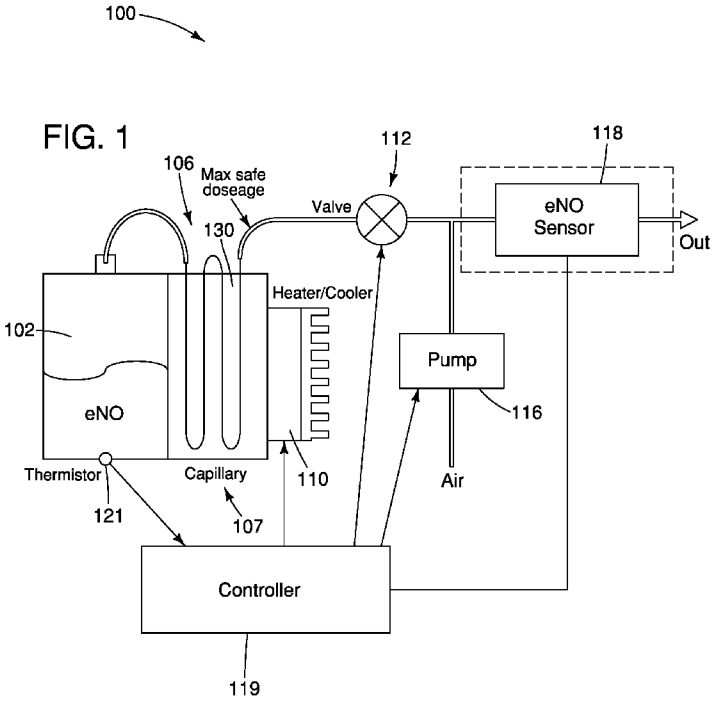
(71) Applicant: **CASE WESTERN RESERVE UNIVERSITY** [US/US]; 10900 Euclid Avenue, Cleveland, OH 44106 (US).

(72) Inventor: **STAMLER, Jonathan, S.**; 19401 South Park Boulevard, Shaker Heights, OH 44122 (US).

(74) Agent: **DARE, Heidi, A.**; Brinks Gilson & Lione, P.O. Box 10087, Chicago, IL 60610 (US).

(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, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, 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, SA,

(54) Title: VAPORIZATION SYSTEM FOR DELIVERY IN A CONTROLLED CONCENTRATION



(57) Abstract: Devices for delivering a controlled concentration of an agent are provided. The device includes a reservoir for the agent and a flow control portion operably connected to the reservoir. The device also includes a valve for releasing the agent from the flow control portion and a pump for flowing air to mix with the agent released by the valve and for flowing the agent and air mixture out of the device. Methods of delivering a vaporized agent to a subject are also provided. The methods include storing a liquid agent in a reservoir of a device and flowing the agent into a flow control chamber to change the agent to a gas. The methods also include mixing the agent in gas form with air and flowing the agent and air mixture out of the device to be delivered to a subject.

WO 2018/226928 A1

[Continued on next page]

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, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, 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, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

VAPORIZATION SYSTEM FOR DELIVERY IN A CONTROLLED CONCENTRATION

RELATED APPLICATIONS

[0001] This application claims the benefit of and priority to, under 35 U.S.C. § **119**(e) of U.S. Provisional Application No. 62/516,973, filed June 8, 2017, the entire contents of which are incorporated herein by reference in its entirety.

FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0002] This invention was made with government support under federal grant number N66001-10-C-2015 awarded by Defense Advanced Research Projects Agency. The government has certain rights in the invention.

BACKGROUND

Technical Field

[0003] This application relates to devices and methods for delivery of a controlled concentration of a substance using a vaporization system, and in particular to devices and methods for ambulatory vaporization systems for delivering a nitrosylating agent.

Background Information

[0004] Administration of ethyl nitrite (ENO) gas is currently cumbersome and not amenable to ambulatory care. Typically a large tank of ENO gas is needed for delivery of the ENO gas to a subject and the tank is not readily movable by the subject receiving the ENO gas. In addition, the concentration of the ENO delivered to the subject must be controlled so that the ratio of ENO to hemoglobin is regulated.

[0005] What is needed is a system and a method for delivering a substance in a controlled concentration that allows for ambulation of the subject receiving the controlled concentration of the substance. What is needed is a system and a

method for delivering ENO at concentrations in the range of about 0.1-100 ppm using a device that allows patient mobility.

BRIEF SUMMARY

[0006] Devices and methods for delivering a controlled concentration of an agent are provided. The device includes a reservoir for the agent and a flow control portion operably connected to the reservoir. The device also includes a valve for releasing the agent from the flow control portion and a pump for flowing air to mix with the agent released by the valve and for flowing the agent and air mixture out of the device.

[0007] In another aspect, methods of delivering a vaporized agent to a subject are provided. The methods include storing a liquid agent in a reservoir of a device and flowing the agent into a flow control chamber to change the agent to a gas. The methods also include mixing the agent in gas form with air and flowing the agent and air mixture out of the device to be delivered to a subject.

[0008] In another aspect, the present disclosure relates to a device for delivering a controlled concentration of an agent, the device comprising: (a) a reservoir for the agent; (b) a flow control portion operably connected to the reservoir; (c) a valve for releasing the agent from the flow control portion; and (d) a pump for flowing air to mix with the agent released by the valve and for flowing the agent and air mixture out of the device.

[0009] In one embodiment, the flow control portion comprises a capillary tubing system. In one embodiment, the length of the capillary tubing system is about 1 mm to about 1000 mm.

[0010] In another embodiment, the flow control portion of the device comprises a gas expansion chamber.

[0011] In yet another embodiment, the device further comprises a manifold operably connected to the flow control portion.

[0012] In yet another embodiment, the device further comprises a temperature control unit.

[0013] In another embodiment, the device further comprises a controller for controlling the flow of the agent through the device. In one embodiment, the controller controls the pump and/or the temperature.

[0014] In another embodiment, the reservoir of the device comprises a replaceable cartridge.

[0015] In yet another embodiment, the reservoir of the device comprises stainless steel.

[0016] In another embodiment, the device further comprises a portion of a manifold that co-extends along at least a portion of the reservoir.

[0017] In another embodiment, the device further comprises a battery.

[0018] In another embodiment, the device further comprises an agent, wherein the agent comprises liquid ethyl nitrite.

[0019] Another aspect of the present disclosure relates to a method of delivering a vaporized agent to a subject, the method comprising: (a) storing a liquid agent in a reservoir of a device; (b) flowing the agent into a flow control chamber to change the agent to a gas; (c) mixing the agent in gas form with air; and (d) flowing the agent and air mixture out of the device to be delivered to a subject.

[0020] In one embodiment, the method further comprises heating the liquid agent.

[0021] In another embodiment, the method comprises delivering the agent to the subject at a range of about 0.1-100 ppm.

[0022] In yet another embodiment, the agent used in the method comprises liquid ethyl nitrite.

[0023] In another embodiment, the method further comprises controlling the amount of the agent delivered to the subject by controlling the temperature of the device.

[0024] In yet another embodiment, the method further comprises controlling flow out of the flow control chamber with a valve.

[0025] In another embodiment, the device used in the method for delivering the agent to the subject is an ambulatory device.

BRIEF DESCRIPTION OF THE DRAWINGS

[0026] **FIG. 1** is a schematic of an embodiment of an ambulatory device.

[0027] **FIG. 2A** is a top view of an embodiment of an ambulatory device.

[0028] **FIG. 2B** is a top view of the device shown in FIG. 2A with the casing in an open configuration.

[0029] **FIG. 2C** is a top view of the device shown in FIG. 2A with the casing in a closed configuration.

[0030] **FIG. 3A** illustrates an embodiment of an ambulatory device with a delivery device connected to the ambulatory device.

[0031] **FIG. 3B** is a perspective top view of the ambulatory device shown in FIG. 3A.

[0032] **FIG. 3C** is a perspective bottom view of the device shown in FIG. 3A.

[0033] **FIG. 4** is a top view comparing two embodiments of an ambulatory device.

[0034] **FIG. 5** illustrates a replaceable reservoir of an embodiment of an ambulatory device.

[0035] **FIG. 6** is a sectional view an embodiment of an ambulatory device.

[0036] **FIG. 7** is a perspective view of an embodiment of an ambulatory device shown without a casing.

[0037] **FIG. 8** is a schematic of an embodiment of an ambulatory device.

[0038] **FIG. 9** is a schematic of an embodiment of an ambulatory device.

DETAILED DESCRIPTION

[0039] The embodiments disclosed below are not intended to be exhaustive or to limit the scope of the disclosure to the precise form in the following description. Rather, the embodiments are chosen and described as examples so that others skilled in the art may utilize its teachings.

[0040] Unless specifically stated, as used herein, the term “about” refers to a range of values ± 10% of a specified value. For example, the phrase “about 200" includes ± 10% of 200, or from 180 to 220. When stated otherwise the term about will refer to a range of values that include ± 20%, ± 10%, or ± 5%, etc.

[0041] A schematic view of an embodiment of an ambulatory device **100** for delivery of controlled concentration of a substance is shown in FIG. 1. In some embodiments, the device may be used to deliver a nitrosylating agent to a subject. The nitrosylating agent includes but is not limited to the following: ethyl nitrite, amyl nitrite, butyl nitrite, isobutyl nitrite, tert-butyl nitrite and combinations thereof. In some embodiments, the nitrosylating agent is ethyl nitrite (ENO). The device **100** shown in FIG. 1 is described with reference to ENO as the agent being delivered, however, other agents may also be used. For example, any liquid agent that may be vaporized for delivery to a subject may be delivered using the device **100**. The temperature, delivery rate and controller will depend on the agent being delivered.

[0042] The device **100** includes a reservoir **102** for storing the agent. The reservoir **102** may be connected to a flow control portion **106** such as a manifold **130** and a capillary tubing system **107** shown in FIG. 1 or a gas expansion chamber **209** (shown in FIG. 8). A temperature controller **110** may be connected to the flow control portion **106**. One or more valves **112** control the flow of agent out of the flow control portion **106** to be mixed with fresh air and delivered to the subject. In some embodiments, a pump **116** may be used to pump the air mixed with the agent. A sensor **118** may be included to monitor or control the amount of the agent that is delivered to the subject. A controller **119** may be included in the device **100** to monitor and regulate the temperature of the reservoir **102**, the temperature controller **110**, the valve **112**, the pump **116** and the sensor **118**. In some embodiments, a thermistor **121** may be connected to the reservoir **102** and the controller **119**.

[0043] FIG. 2A shows the device **100** assembled together in a casing **120**. FIG. 2B shows an open view of the assembled device **100** within the casing **120**. Note that insulation that may also be provided is not shown. FIG. 2C shows a top view of the device **100** enclosed in the casing **120**. As shown in FIG. 2A, the device **100** may include a reservoir **102** that stores ENO in a mixed phase (liquid and saturated gas) storage cartridge; storage in liquid form allows for a considerable amount of agent to be included in the device **100** relative to the rate

of use. The storage cartridge may be made of steel, such as stainless steel or a polymer, such as polycarbonate. In some embodiments, a stainless steel reservoir **102** may be used to improve the thermal conduction between the temperature controller **110** and the reservoir **102**. The boiling point of ENO is 63° F so as a result the vapor pressure generated at temperatures above this point self-propel ENO through the system. In addition, the vapor pressure of ENO is proportional to temperature thus ENO flow may be controlled by the device **100** temperature. As shown in FIG. 2A, the device **100** may include a replaceable cartridge, such as a replaceable ENO cartridge **102**. An example of a replaceable cartridge **102** is shown in FIG. 5. The replaceable cartridge **102** may be exchanged through the use of a double shut-off system **124** for quick recharging/re-dosing. The double shutoff system **124** serves to prevent ENO leakage while the mating half-closes to keep contaminates out of the system during a vial exchange. When a replaceable reservoir **102** is included, a release **126** may be include to release the reservoir from the casing **120**. The replaceable cartridge **102** may have an internal volume of about 20 ml and be designed to hold about 10 ml of liquid ENO. The remaining 10 ml of dead-space ensures sufficient volume to allow a relatively large amount of saturated vapor to develop for release into the flow control portion **106**. In addition, the dead-space reduces the chances of injecting liquid into the flow control portion **106**.

[0044] In some embodiments, the replaceable cartridge can have an internal volume of about 1 ml to about 1000 ml. In other embodiments, the replaceable cartridge can have an internal volume of about 1 to about 900 ml, about 1 to about 800 ml, about 1 to about 700 ml, about 1 to about 600 ml, about 1 to about 500 ml, about 1 to about 400 ml, about 1 to about 300 ml, about 1 to about 200 ml, about 1 to about 100 ml, about 1 to about 50 ml, or about 1 to about 20 ml. In other embodiments, the replaceable cartridge can have an internal volume of about 1 to about 100 ml, about 100 to about 200 ml, about 300 to about 400 ml, about 400 to about 500 ml, about 500 to about 600 ml, about 700 to about 800 ml, about 800 to about 900 ml, or about 900 to about 1000 ml. In other embodiments, the replaceable cartridge can have an internal volume of about 1

to about 100 ml, about 10 to about 100 ml, about 10 to about 50 ml, about 10 to about 40 ml, about 10 to about 30 ml, or about 10 to about 20 ml.

[0045] As shown in FIG. 2A, the device **100** may also include a manifold **130**. The manifold **130** may be a small block of metal, such as stainless steel. The reservoir **102** feeds into the manifold **130** through a quick disconnect fitting **132**. From the fitting **132**, the manifold **130** feeds the agent from the reservoir **102** into and then back out of the capillary tubing system **107**. Finally the manifold **130** interfaces the solenoid valve's inlet and outlet **112** with the now gaseous agent exiting through a small Teflon tube to join with the fresh air at an outlet fitting **133**. An outlet connector **135** may extend to the exterior of the casing **120** for attachment of a delivery device for the subject as described below with reference to FIG. 3A. FIG. 7 shows the device **100** assembled together and without the casing.

[0046] As discussed above, some embodiments of the device **100** may include the capillary tubing system **107** that receives the gaseous agent from the reservoir **102**. The capillary tubing system **107** may be made of fused silica glass with a polymer coating to aid handling and connections. Both the inner diameter (ID) and the length can be varied for large scale changes in agent delivery (i.e. swapping one tube assembly for another). The internal diameter (ID) of the capillary tubing system may be from about 10 microns to about 500 microns. In some embodiments, the ID is between 10 and 20 microns. This diameter severely restricts gas flow to achieve the desired dose range of the agent. For example, when ENO is used as the agent, the dose range is about 0.1-100 ppm. For any given tube, closely-controlling the temperature of the reservoir **102** and the capillary tubing system **107**, allows for system pressure and thus flow to be tightly regulated. In some embodiments, the length of the capillary tubing system **107** may also be varied to control the delivery of the agent. The length of the capillary tubing system may be about 1 mm to about 1000 mm. In some embodiments, the capillary tubing system may be provided as a coil. In an example embodiment using ENO liquid as the starting agent, a capillary tube that was 95 mm long with a 20 micron ID delivered about 20 ppm to about 45 ppm

ENO as the internal system was heated. In another example embodiment, a capillary tube that was 135 mm long with a 20 micron ID delivered about 3.8-10.5 ppm ENO over a temperature range of 75° F to 87° F.

[0047] In some embodiments, the dose range is about 0.1 ppm to about 100 ppm, 1 ppm to about 100 ppm, about 0.1 ppm to about 50 ppm, or about 50 ppm to about 100 ppm. In other embodiments, the dose range is about 0.1 ppm to about 10 ppm, about 0.1 ppm to about 20 ppm, about 0.1 ppm to about 30 ppm, about 0.1 ppm to about 40 ppm, about 0.1 ppm to about 50 ppm, about 0.1 ppm to about 60 ppm, about 0.1 ppm to about 70 ppm, about 0.1 ppm to about 80 ppm, about 0.1 ppm to about 90 ppm, or about 0.1 ppm to about 100 ppm. In other embodiments, the dose range is about 0.1 ppm to about 20 ppm, about 10 ppm to about 30 ppm, about 20 ppm to about 40 ppm, about 30 ppm to about 50 ppm, about 40 ppm to about 60 ppm, about 50 ppm to about 70 ppm, about 60 ppm to about 80 ppm, about 70 ppm to about 90 ppm, or about 80 ppm to about 100 ppm.

[0048] In some embodiments, the dose range is about 0.1 ppm to about 30 ppm, about 1 ppm to about 30 ppm, about 10 ppm to about 40 ppm, about 20 ppm to about 50 ppm, about 30 ppm to about 60 ppm, about 40 ppm to about 70 ppm, about 50 ppm to about 80 ppm, about 60 ppm to about 90 ppm, or about 70 ppm to about 100 ppm.

[0049] In some embodiments, the internal diameter (ID) of the capillary tubing system is about 10 microns to about 20 microns, about 20 microns to about 30 microns, about 30 microns to about 40 microns, about 40 microns to about 50 microns, about 50 microns to about 60 microns, about 60 microns to about 70 microns, about 70 microns to about 80 microns, about 80 microns to about 90 microns, about 90 microns to about 100 microns, about 100 microns to about 110 microns, about 110 microns to about 120 microns, about 120 microns to about 130 microns, about 130 microns to about 140 microns, about 140 microns to about 150 microns, about 150 microns to about 160 microns, about 160 microns to about 170 microns, about 170 microns to about 180 microns, about 180 microns to about 190 microns, about 190 microns to about 200 microns, about

200 microns to about 210 microns, about 210 microns to about 220 microns, about 220 microns to about 230 microns, about 230 microns to about 240 microns, about 240 microns to about 250 microns, about 150 microns to about 260 microns, about 260 microns to about 270 microns, about 270 microns to about 280 microns, about 280 microns to about 290 microns, about 290 microns to about 300 microns, about 300 microns to about 310 microns, about 310 microns to about 320 microns, about 320 microns to about 330 microns, about 330 microns to about 340 microns, about 340 microns to about 350 microns, about 350 microns to about 360 microns, about 360 microns to about 370 microns, about 370 microns to about 380 microns, about 380 microns to about 390 microns, about 390 microns to about 400 microns, about 400 microns to about 410 microns, about 410 microns to about 420 microns, about 420 microns to about 430 microns, about 430 microns to about 440 microns, about 440 microns to about 450 microns, about 450 microns to about 460 microns, about 460 microns to about 470 microns, about 470 microns to about 480 microns, about 480 microns to about 490 microns, or about 490 microns to about 500 microns.

[0050] In some embodiments, the internal diameter (ID) of the capillary tubing system is about 10 microns to about 50 microns, about 50 microns to about 100 microns, about 100 microns to about 150 microns, about 150 microns to about 200 microns, about 200 microns to about 250 microns, about 250 microns to about 300 microns, about 300 microns to about 350 microns, about 350 microns to about 400 microns, about 400 microns to about 450 microns, or about 450 microns to about 500 microns. In other embodiments, the internal diameter (ID) of the capillary tubing system is about 10 microns to about 100 microns, about 100 microns to about 200 microns, about 200 microns to about 300 microns, about 300 microns to about 400 microns, or about 400 microns to about 500 microns.

[0051] In some embodiments, the length of the capillary tubing system is about 1 mm to about 500 mm, about 1 mm to about 400 mm, about 1 mm to about 300 mm, about 1 mm to about 200 mm, or about 1 mm to about 100 mm. In other embodiments, the length of the capillary tubing system is about 1 mm to about

100 mm, about 100 mm to about 200 mm, about 200 mm to about 300 mm, about 300 mm to about 400 mm, or about 400 mm to about 500 mm.

[0052] The temperature controller **110** and the thermistor **121** may be used to control the device **100** internal temperature. The temperature controller **110** may be a thermoelectric cooler (TEC) that is a solid-state active heat pump. By passing current through the TEC a temperature difference is realized between the two sides. The TEC is reversible, which allows the device **100** to be heated or cooled depending upon ambient conditions. In addition, the device **100** is arranged such that the capillary tubing system **107** is at a slightly higher temperature than the reservoir **102** (due to the closer proximity of the capillary tube system **107** to the TEC). This gradient creates slightly higher pressures in the downstream side of the capillary tubing system **107**, which pushes any condensate back up the capillary tubing system **107** towards the reservoir **102** behind the flowing gas. It also serves as a safety feature: if some liquid agent were to be expelled into the capillary tubing system, the liquid agent would still vaporize by the time the liquid agent flowed out of the capillary tubing system **107**.

[0053] After the exiting the capillary tubing system **107**, the agent passes through a solenoid driven control valve **112**; this is the secondary means to control agent delivery. The valve **112** is principally used in its ON/OFF operation but can be used in a Pulse Width Modulation for additional flow control including incorporation of an on-demand function (e.g. switched to open upon sensing subject's inspiration). At rest, the valve **112** is closed. This is a second safety feature in that if there is a power failure no agent can be released. The agent in vapor form then flows into a junction where vapor agent is mixed with fresh air supplied by a reciprocating diaphragm of the pump **116**. The pump speed can be varied to regulate the concentration and total flow rate of the agent/air mixture out of the device **100**. The gas blend then passes into a delivery device **140** to be administered to the subject. As shown in FIG. 3 A, the delivery device **140** may be a nasal cannula. Any type of delivery device **140** known in the art for delivering a gas to a subject may be used with the device **100**. By way of non-

limiting example, when ENO is used, the gas delivered may be about 0.1-100 ppm ENO in air.

[0054] The device **100** may include a controller **119** that operates all of the various subsystems. The controller **119** maintains the correct temperature (thermistor feedback), operates the solenoid valve **112** and the air pump **116**. The device **100** may also include a power source **138** such as a battery. By way of non-limiting example, the power source **138** may be a two cell (7.4V nominal voltage) Lithium Polymer battery. The battery **138** presently occupies about half of the internal volume of the device **100**. Lithium Polymer provides high power density for a secondary (rechargeable) cell. A 5000mAh battery will run the device **100** for 8+ hours depending on ambient temperatures. The software is a simple menu-based controller that drives the various sub-systems. An ARM Cortex M3 processor, the STM32L151, is used because it is small, low power, and has on-board Digital-to-Analog outputs as well as advanced timers. The source code was compiled with GCC using Rowley's Crossworks for ARM software.

[0055] FIGS. 3B and 3C show exterior views of an embodiment of the device **100**. FIG. 3B shows a top view of the device **100** that may include a display **150** and control buttons **152**. The display **150** may be used to give the subject feedback from the device **100** and/or to view settings. In some embodiments, the control buttons **152** may be used for programing the device **100**, to select different preset programs, to change the display **150**, and the like. By way of non-limiting example, the flow rate from the device **100** may be controlled by temperature of the reservoir **102**, the valve **112**, and the pump **116,** and the controller **130** may be used to regulate each of the components to deliver the agent at a specified amount. As shown in FIG. 3B, the device **100** may also include a heat sink **154** to facilitate control of the temperature of the agent for delivery through the device **100**. FIGS. 3B and 3C also show a door **156** that provides access to the reservoir **102**, for example when a replaceable cartridge is used to supply the agent as described above. FIG. 3C also illustrates a battery cover **160**. FIG. 6 illustrates a sectional view of the device **100** with the casing

120 included. In some embodiments, insulation may also be included in the casing **120**.

[0056] FIG. 4 illustrates the device **100** having two different configurations for the manifold **130**. The device **100** on the right illustrates a manifold extension **130a** that co-extends along a portion of the reservoir **102**. In some embodiments, the manifold extension **130a** is included to facilitate thermal conduction and even distribution of the temperature control in the reservoir **102** and control flow through the capillary tubing system **107**.

[0057] In some embodiments, the device **100** may deliver the agent in an amount of about 0.1-100 ppm. In some embodiments, the agent delivered is in an amount of about 0.1 ppm to about 100 ppm, about 0.1 ppm to about 10 ppm, about 0.1 ppm to about 20 ppm, about 0.1 ppm to about 30 ppm, about 0.1 ppm to about 40 ppm, about 0.1 ppm to about 50 ppm, about 0.1 ppm to about 60 ppm, about 0.1 ppm to about 70 ppm, about 0.1 ppm to about 80 ppm, or about 0.1 ppm to about 90 ppm. In other embodiments, the agent delivered is in an amount of about 1 ppm to about 10 ppm, about 1 ppm to about 20 ppm, about 1 ppm to about 30 ppm, about 1 ppm to about 40 ppm, about 1 ppm to about 50 ppm, about 1 ppm to about 60 ppm, about 1 ppm to about 70 ppm, about 1 ppm to about 80 ppm, about 1 ppm to about 90 ppm, or about 1 ppm to about 100 ppm.

[0058] In other embodiments, the agent delivered is in an amount of about 0.1 ppm to about 20 ppm, about 5 ppm to about 25 ppm, about 10 ppm to about 30 ppm, about 15 ppm to about 35 ppm, about 20 ppm to about 40 ppm, about 25 ppm to about 45 ppm, about 30 ppm to about 50 ppm, about 35 ppm to about 55 ppm, about 40 ppm to about 60 ppm, about 45 ppm to about 65 ppm, about 50 ppm to about 70 ppm, about 55 ppm to about 75 ppm, about 60 ppm to about 80 ppm, about 65 ppm to about 85 ppm, about 70 ppm to about 90 ppm, about 75 ppm to about 95 ppm, or about 80 ppm to about 100 ppm, In other embodiments, the agent delivered is in an amount of about 0.1 ppm to about 30 ppm, about 1 ppm to about 30 ppm, about 10 ppm to about 40 ppm, about 20 ppm to about 50 ppm, about 30 ppm to about 60 ppm, about 40 ppm to about 70 ppm, about 50

ppm to about 80 ppm, about 60 ppm to about 90 ppm, or about 70 ppm to about 100 ppm. In other embodiments, the agent delivered is in an amount of about 0.1 ppm to about 40 ppm, about 1 ppm to about 40 ppm, about 10 ppm to about 50 ppm, about 20 ppm to about 60 ppm, about 30 ppm to about 70 ppm, about 40 ppm to about 80 ppm, about 50 ppm to about 90 ppm, or about 60 ppm to about 100 ppm.

[0059] In some embodiments, the device **100** may be designed to have 2 or more ranges for delivery that may be preset or controlled by the subject. For example, the device **100** may deliver the agent in a first range of about 0.1-10 ppm and a second range of about 1-100 ppm.

[0060] The amount of ENO exiting the device **100** may be quantified using Fourier transformed infra-red spectroscopy (FTIR). The device **100** delivered increasing amounts of ENO in response to raising the temperature. The capillary action draws ENO through the capillary tubing system **107** at a fixed, but temperature dependent rate. By controlling the temperature of the ENO in the device **100**, the amount of ENO delivered to the subject is controlled.

[0061] FIGS. 8 and 9 illustrate schematic views of alternative embodiments of an ambulatory device **200**. Similar to the device **100** described above, the device **200** may be used to deliver a nitrosylating agent to a subject. The nitrosylating agent includes but is not limited to the following: ethyl nitrite, amyl nitrite, butyl nitrite, isobutyl nitrite, tert-butyl nitrite and combinations thereof. In some embodiments, the nitrosylating agent is ethyl nitrite (ENO). However, any liquid agent that may be vaporized for delivery to a subject may be delivered using the device **200**. The temperature, delivery rate and controller will depend on the agent being delivered.

[0062] The device **200** includes a reservoir **202** for storing the agent to be delivered. The agent may be in liquid form in the reservoir **202**. The reservoir **202** may be connected to a flow control portion **206** such as a gas expansion chamber **209**. The device **200** may include all the features of the device **100** described above with the exception that the flow control portion **206** is a gas expansion chamber instead of a capillary tubing system described above. A

temperature controller **210** may be included to control the temperature of the reservoir **202** and/or the gas expansion chamber **209**. In some embodiments, no temperature control is included. A pressure gauge **211** may be included to monitor the pressure in the reservoir **202** and a pressure regulator **213** may be used to control the flow of the agent from the reservoir **202** to the gas expansion chamber **209**. One or more valves **212** control the flow of agent out of the flow control portion **206** to be delivered to the subject. In some embodiments, a pump **216** may be used to pump the air mixed with the agent. A sensor **218** may be included to monitor or control the amount of the agent that is delivered to the subject. A controller **219** (including, but not limited to, a microcontroller) may be included in the device **200** to monitor and regulate the temperature of the reservoir **202**, the temperature controller **210**, the valve **212**, the pump **216** and the sensor **218**.

[0063] The device **200** may include a reservoir **202** that stores ENO in a mixed phase (liquid and saturated gas) storage cartridge; storage in liquid form allows for a considerable amount of agent to be included in the device **200** relative to the rate of use. The storage cartridge may be made of steel, such as stainless steel or a polymer, such as polycarbonate. In some embodiments, a stainless steel reservoir **202** may be used to improve the thermal conduction between the temperature controller **210** and the reservoir **202**. Similar to the device **100**, ENO flow may be controlled by the temperature of the device **200**. The device **200** may include a replaceable cartridge, such as a replaceable ENO cartridge **202**.

[0064] After exiting the flow control portion **206**, the agent passes through a solenoid driven control valve **212**. A flow restrictor **215** may also be included in the device **200** between the flow control portion **206** and the control valve **212**. The valve **212** is principally used in its ON/OFF operation but can be used in a Pulse Width Modulation for additional flow control including incorporation of an on-demand function (e.g. switched to open upon sensing subject's inspiration). At rest, the valve **212** is closed. The agent in vapor form then flows into a junction where vapor agent is mixed with fresh air **217** supplied by the pump **216**. The pump speed can be varied to regulate the concentration and total flow rate of the

agent/air mixture out of the device **200**. The gas blend then passes into a delivery device **240** to be administered to the subject. Any type of delivery device **240** known in the art for delivering a gas to a subject may be used with the device **200**. By way of non-limiting example, when ENO is used, the gas delivered may be about 0.1-100 ppm ENO in air. In some embodiments, the gas delivered is about 0.1 ppm to about 100 ppm, about 0.1 ppm to about 10 ppm, about 0.1 ppm to about 20 ppm, about 0.1 ppm to about 30 ppm, about 0.1 ppm to about 40 ppm, about 0.1 ppm to about 50 ppm, about 0.1 ppm to about 60 ppm, about 0.1 ppm to about 70 ppm, about 0.1 ppm to about 80 ppm, or about 0.1 ppm to about 90 ppm. In other embodiments, the gas delivered is about 1 ppm to about 10 ppm, about 1 ppm to about 20 ppm, about 1 ppm to about 30 ppm, about 1 ppm to about 40 ppm, about 1 ppm to about 50 ppm, about 1 ppm to about 60 ppm, about 1 ppm to about 70 ppm, about 1 ppm to about 80 ppm, about 1 ppm to about 90 ppm, or about 1 ppm to about 100 ppm.

[0065] In other embodiments, the gas delivered is about 0.1 ppm to about 20 ppm, about 5 ppm to about 25 ppm, about 10 ppm to about 30 ppm, about 15 ppm to about 35 ppm, about 20 ppm to about 40 ppm, about 25 ppm to about 45 ppm, about 30 ppm to about 50 ppm, about 35 ppm to about 55 ppm, about 40 ppm to about 60 ppm, about 45 ppm to about 65 ppm, about 50 ppm to about 70 ppm, about 55 ppm to about 75 ppm, about 60 ppm to about 80 ppm, about 65 ppm to about 85 ppm, about 70 ppm to about 90 ppm, about 75 ppm to about 95 ppm, or about 80 ppm to about 100 ppm, In other embodiments, the gas delivered is about 0.1 ppm to about 30 ppm, about 1 ppm to about 30 ppm, about 10 ppm to about 40 ppm, about 20 ppm to about 50 ppm, about 30 ppm to about 60 ppm, about 40 ppm to about 70 ppm, about 50 ppm to about 80 ppm, about 60 ppm to about 90 ppm, or about 70 ppm to about 100 ppm. In other embodiments, the gas delivered is about 0.1 ppm to about 40 ppm, about 1 ppm to about 40 ppm, about 10 ppm to about 50 ppm, about 20 ppm to about 60 ppm, about 30 ppm to about 70 ppm, about 40 ppm to about 80 ppm, about 50 ppm to about 90 ppm, or about 60 ppm to about 100 ppm.

[0066] The device **200** may include a controller **219** that operates all of the various subsystems. The controller **219** maintains the correct temperature (thermistor feedback) and operates the solenoid valve **212** and the air pump **216**. The device **200** may also include a power source **238** such as a battery similar to the battery described above.

[0067] Table I shows an example of general device characteristics.

[0068] **Table I: General Device Characteristics**

Specification	Description	Metric	Units	Details / Notes
Physical				
Size	Physical volume of device	175	cm^3	approximately 3.5" x 3" X 1" or similar volume
Weight	Total weight of system	250	g	Goal will be to under this value
Carrying System	How the User will carry or wear device			Belt and MOLLE compatible attachment system
Electrical				
Battery Type	Rechargeable battery pack			Lithium Polymer battery is first choice
Battery Life	Operation time without battery change or charge	24	hr	minimum, longer battery life will depend on final size and weight
Environmental				
Water Proofing	Units ability to tolerate water	IPX 4	N/A	IP Code based; Protected against splashing water - Same as IPX-3 but water is sprayed at all angles. IPX 7 would be water proof to 1m and might be desired
High Temp	Maximum Operation Temp	85	C	
Low Temp	Minimum Operation Temp	-30	C	
Shock Tolerance	Drop distance system must survive	1.5	m	Drop free onto a hard surface
Altitude	Altitude at which the unit will function	sea level - 25000	ft	
User Interface				
Power Switch	Switch that powers the unit on and off			
Input Buttons	For selection of modes and system info			
Interface Screen	Alpha Numeric display for giving user feedback			

Specification	Description	Metric	Units	Details / Notes
Nasal Cannula	For delivery of ENO/Air to user			
Notification system	Way to get the users attention			like small vibrator to notify user of system message (low battery, not breathing through nose, etc)
Drug Delivery				
Range	dosage level the system can deliver	0.1 - 100	ppm	System will be designed for 2 or more ranges spanning 0.1 - 100 ppm, likely will be a 0.1 - 10 ppm and a 1 - 100 ppm ranges.
Accuracy	How close actual dosage is to input value	3	%	This is presently a conservative estimate and need more research
Supply Size	Operation time between ENO recharges	3	day	
On demand	only release ENO on inspiration			

[0069] It is therefore intended that the foregoing detailed description be regarded as illustrative rather than limiting, and that it be understood that it is the following claims, including all equivalents, that are intended to define the spirit and scope of this invention.

CLAIMS

1. A device for delivering a controlled concentration of an agent, the device comprising:

a reservoir for the agent;

a flow control portion operably connected to the reservoir;

a valve for releasing the agent from the flow control portion; and

a pump for flowing air to mix with the agent released by the valve and for flowing the agent and air mixture out of the device.

2. The device according to claim 1, wherein the flow control portion comprises a capillary tubing system.

3. The device according to claim 2, wherein the length of the capillary tubing system is about 1 mm to about 1000 mm.

4. The device according to claim 1, wherein the flow control portion comprises a gas expansion chamber.

5. The device according to any one of claims 1 to 4, further comprising a manifold operably connected to the flow control portion.

6. The device according to any one of claims 1 to 5, further comprising a temperature control unit.

7. The device according to any one of claims 1 to 6, further comprising a controller for controlling the flow of the agent through the device.

8. The device according to claim 7, wherein the controller controls the pump and/or the temperature.

9. The device according to any one of claims 1-8, wherein the reservoir comprises a replaceable cartridge.

10. The device according to any one of claims 1-9, wherein the reservoir comprises stainless steel.

11. The device according to claim 1, further comprising a portion of a manifold that co-extends along at least a portion of the reservoir.

12. The device according to any one of claims 1-11, further comprising a battery.

13. The device according to any one of claims 1-12, further comprising an agent, wherein the agent comprises liquid ethyl nitrite.

14. A method of delivering a vaporized agent to a subject, the method comprising:

storing a liquid agent in a reservoir of a device;

flowing the agent into a flow control chamber to change the agent to a gas;

mixing the agent in gas form with air; and

flowing the agent and air mixture out of the device to be delivered to a subject.

15. The method according to claim 14, further comprising heating the liquid agent.

16. The method according to claim 14 or 15, comprising delivering the agent to the subject at a range of about 0.1-100 ppm.

17. The method according to any one of claims 14-16, wherein the agent comprises liquid ethyl nitrite.

18. The method according to any one of claims 14-17, further comprising controlling the amount of the agent delivered to the subject by controlling the temperature of the device.

19. The method according to any one of claims 14-18, further comprising controlling flow out of the flow control chamber with a valve.

20. The method according to any one of claims 14-19, wherein the device for delivering the agent to the subject is an ambulatory device.

FIG. 1

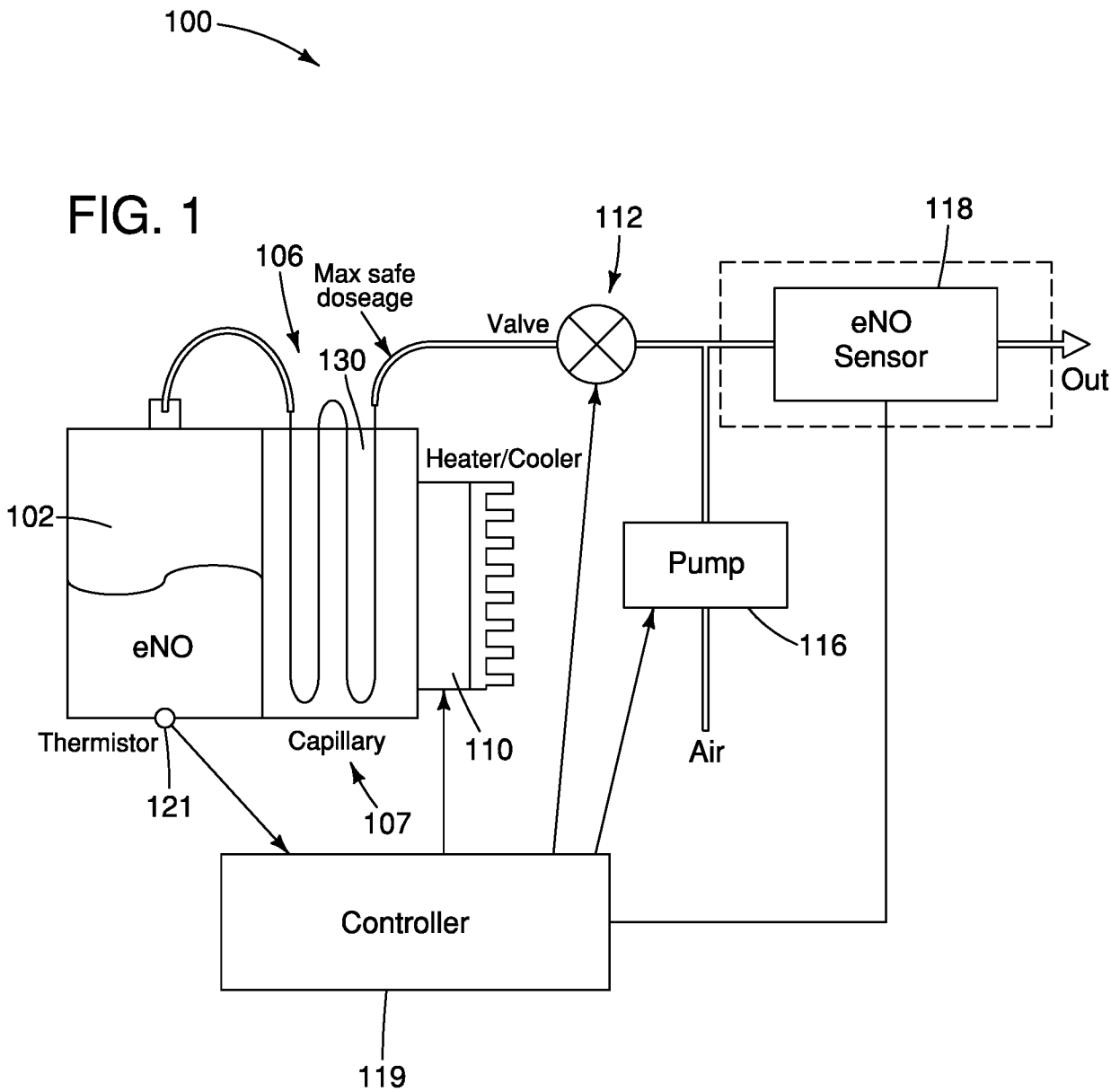

100
106
Max safe doseage
130
112
Valve
118
eNO Sensor
Out
Heater/Cooler
102
eNO
Pump
116
Thermistor
121
Capillary
107
110
Air
Controller
119

FIG. 2A

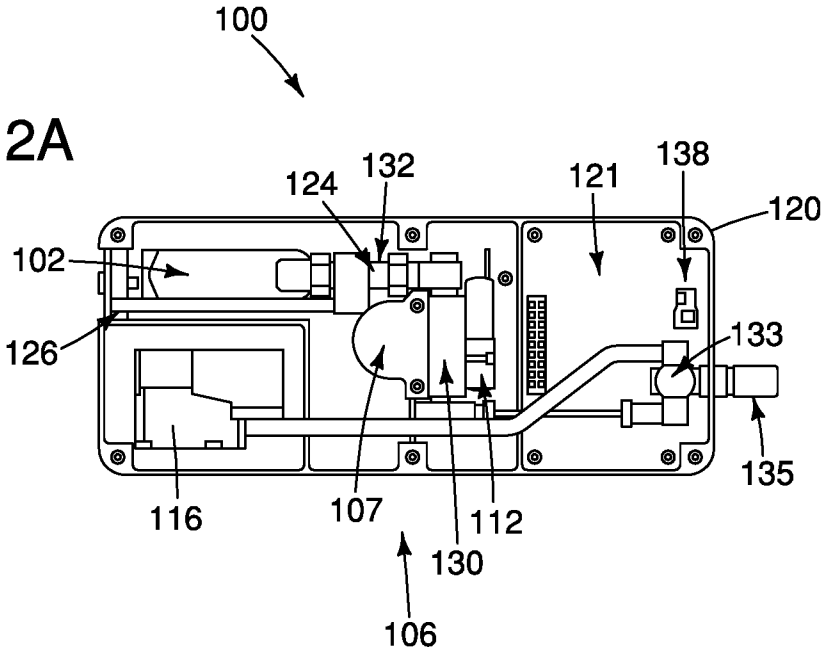


FIG. 2B

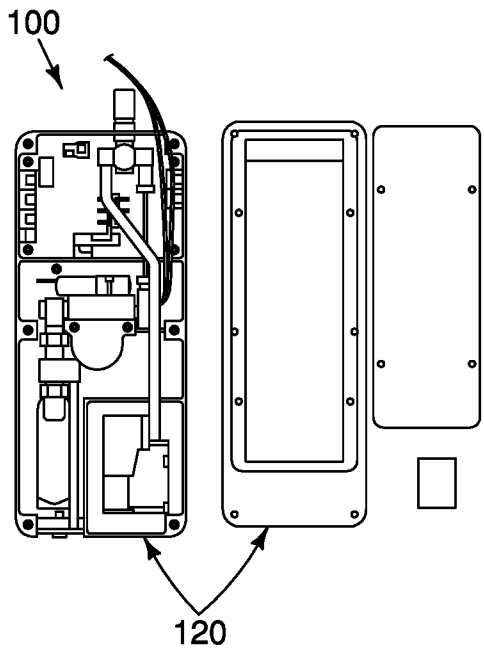
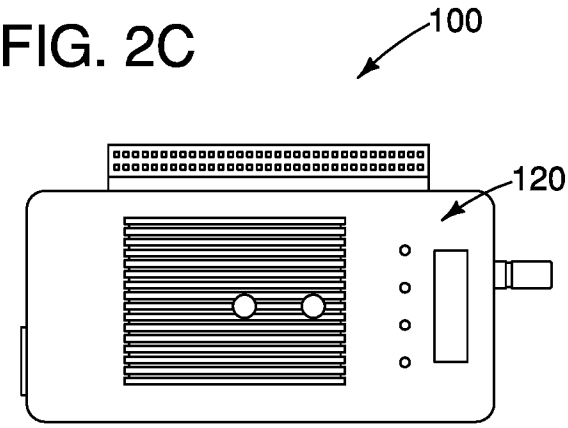


FIG. 2C



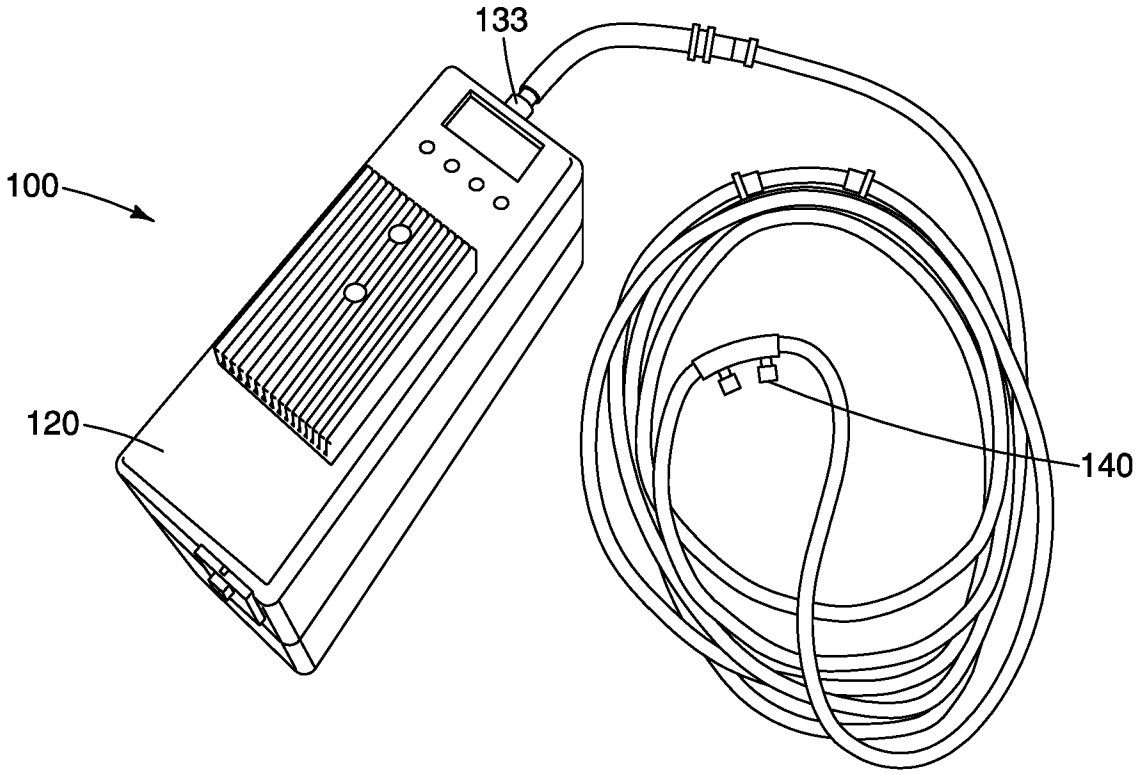


FIG. 3A

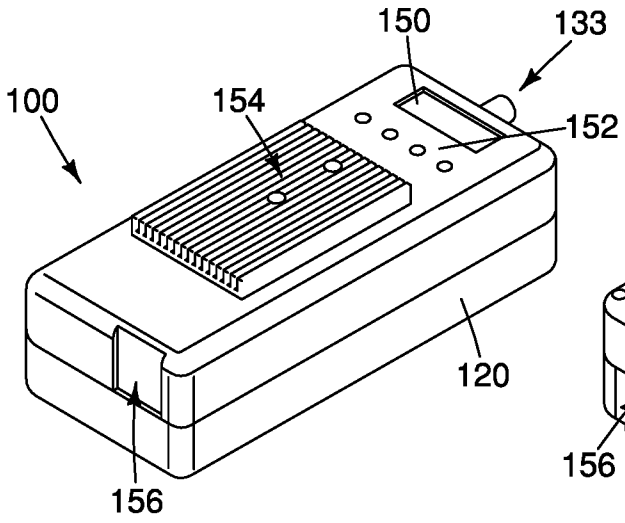


FIG. 3B

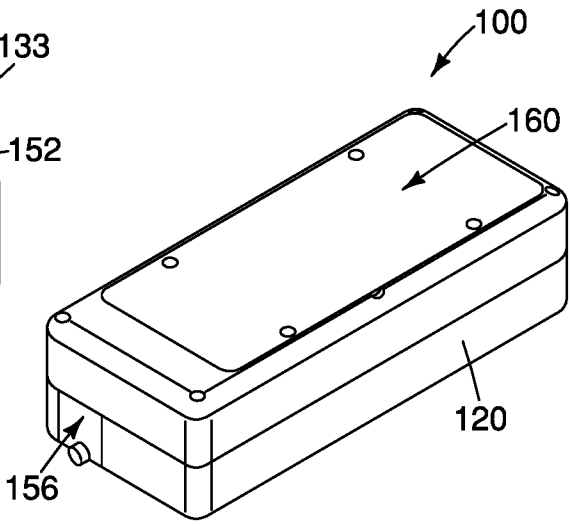


FIG. 3C

FIG. 4

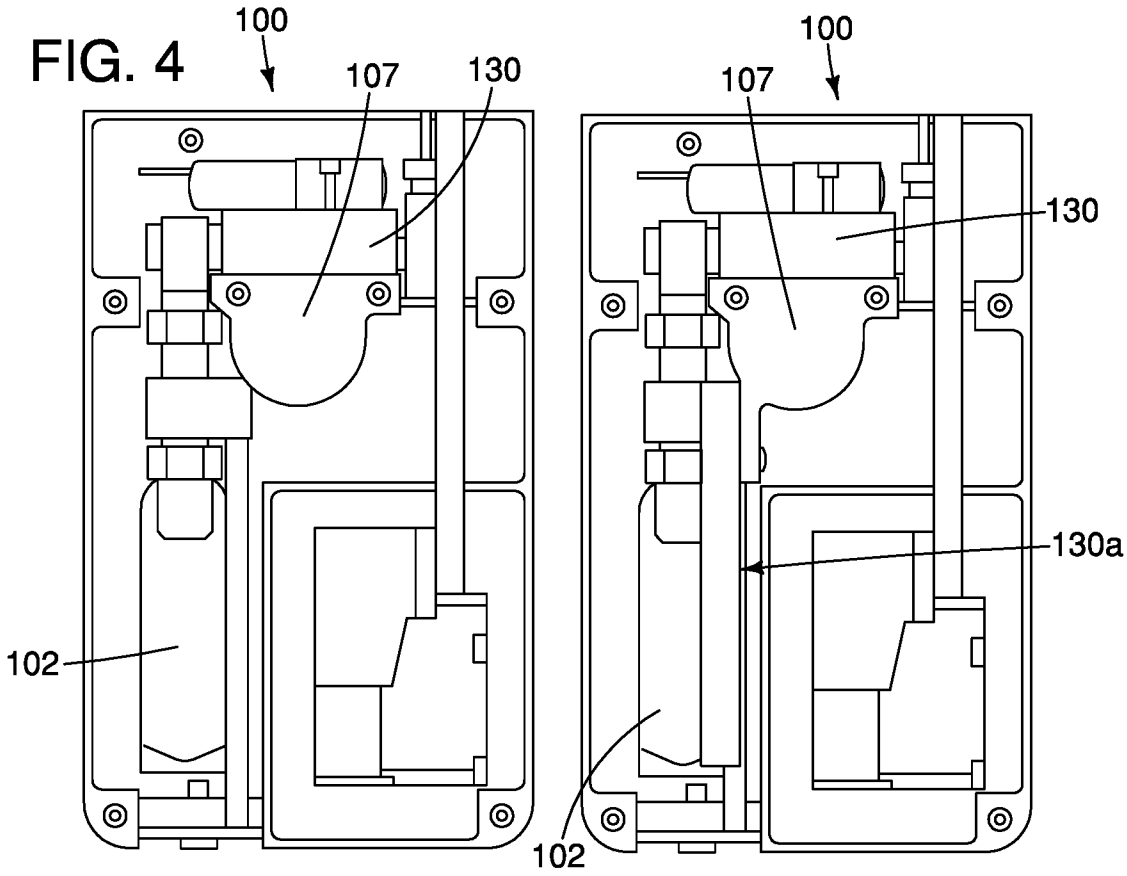
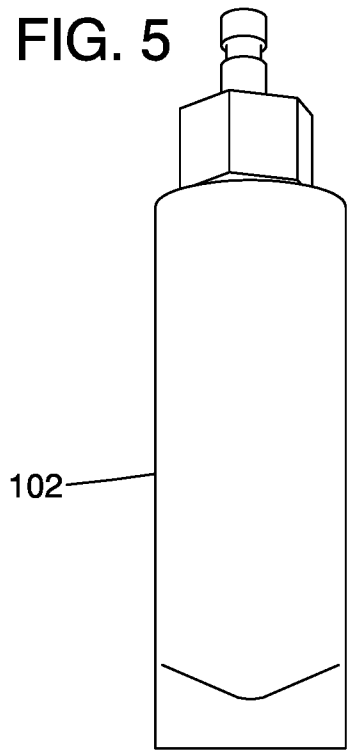


FIG. 5



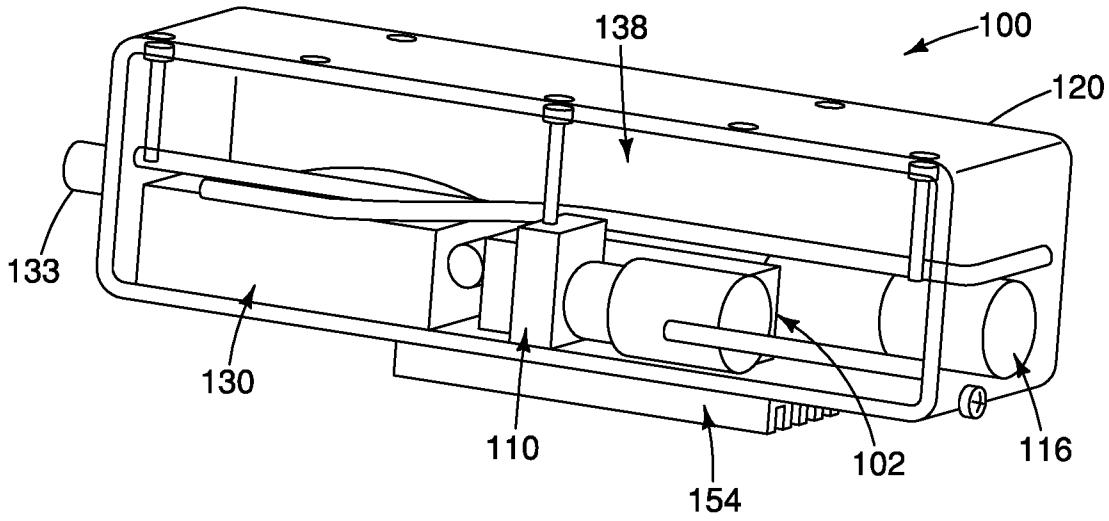

138
100
120
133
130
110
154
102
116

FIG. 6

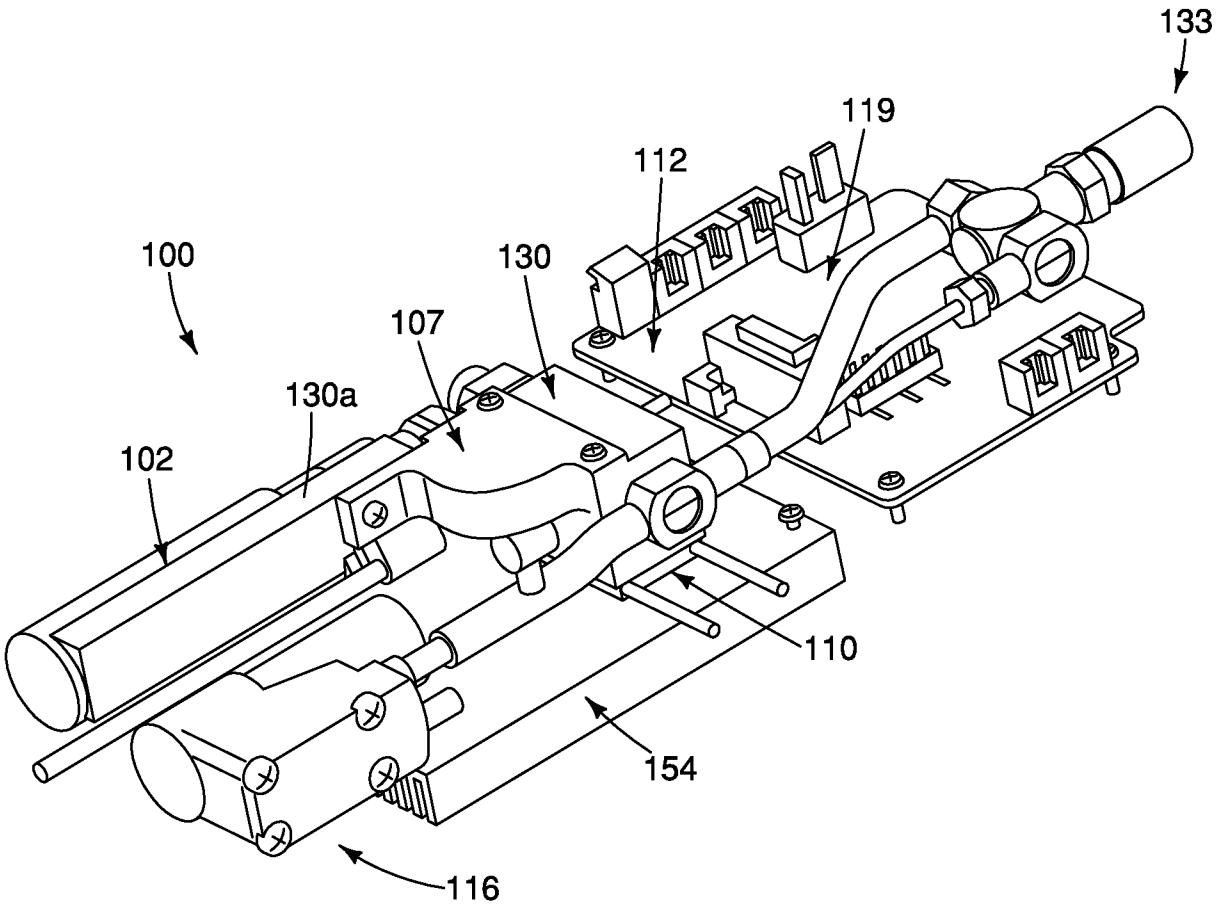

133
119
112
100
130
107
130a
102
110
154
116

FIG. 7

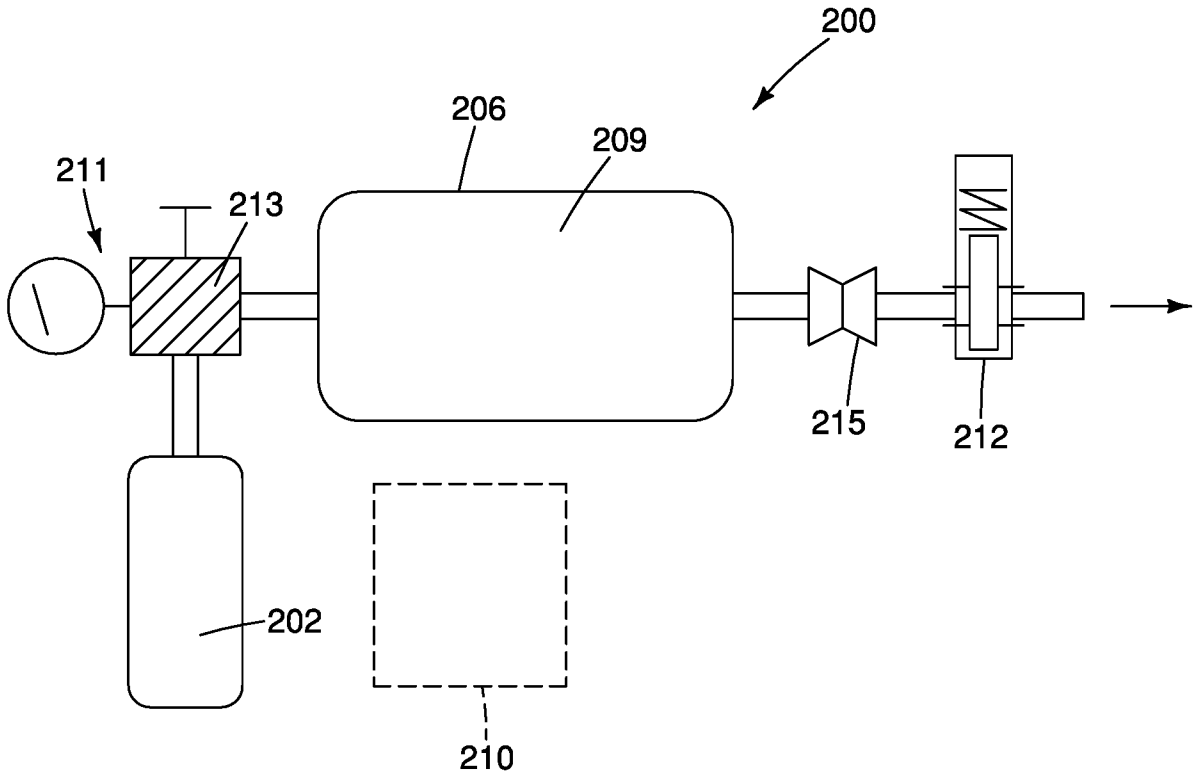


FIG. 8

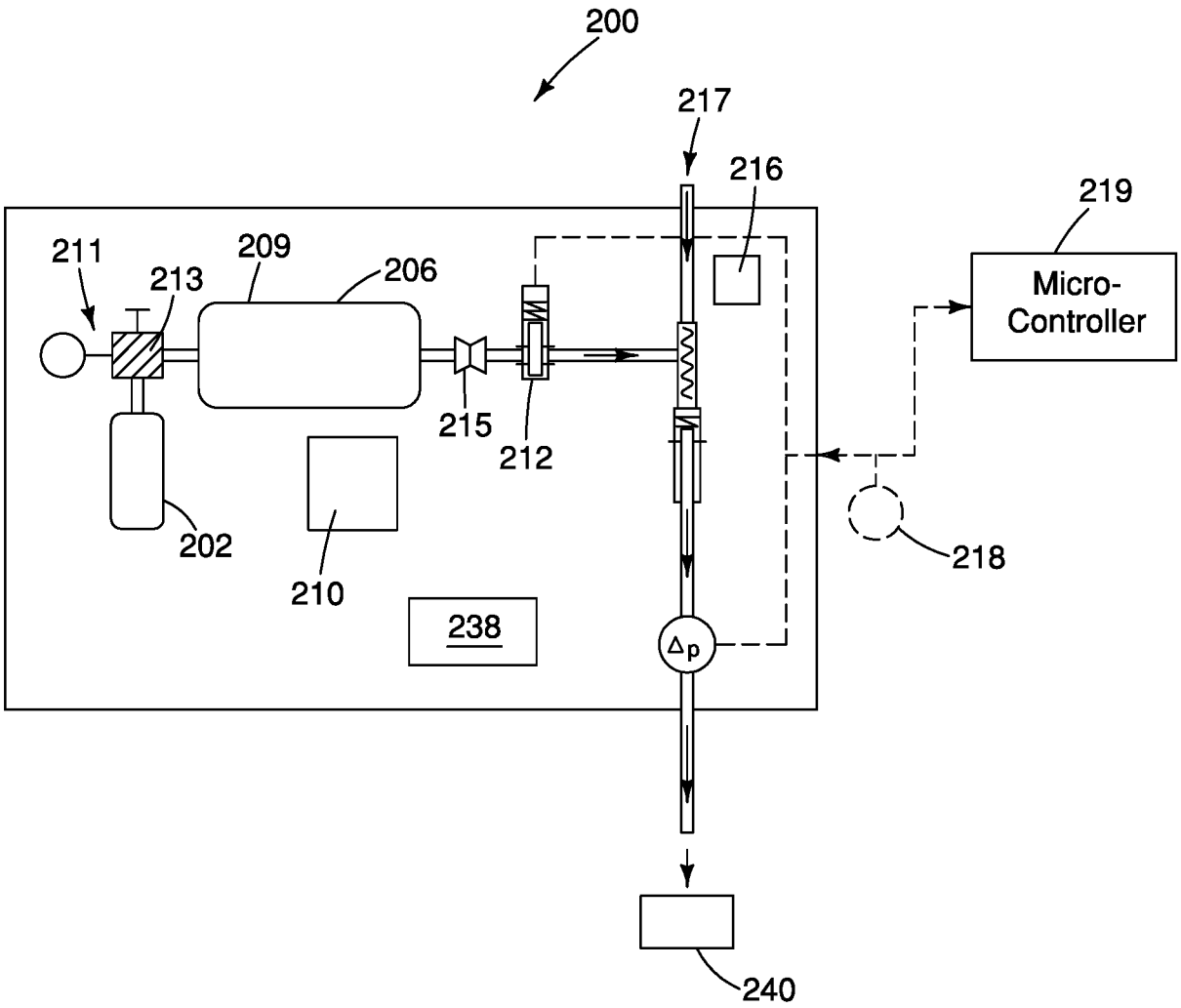

200
217
216
219
Micro-
Controller
211
213
209
206
215
212
202
210
238
Δp
218
240

FIG. 9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2018/036412

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.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 14-20
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:
see FURTHER INFORMATION sheet PCT/ISA/210

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.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/036412

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61M16/00 A61M16/01 A61M16/10 A61M16/12 A61M16/20
A61M11/04 C01B21/20
ADD. A61M16/06
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 C01B

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	WO 2011/063335 A1 (GENO LLC [US]; FINE DAVID H [US]; VASQUEZ GREGORY [US]; JOHNSON BRYAN) 26 May 2011 (2011-05-26)	1-12
Y	figure 1 and 2 paragraph [0023] - paragraph [0042] paragraph [0005] -----	13
X	WO 2012/075420 A1 (GENO LLC [US]; FINE DAVID H [US]; ROSCIGNO ROBERT F [US]; VASQUEZ GREG) 7 June 2012 (2012-06-07) passages of the descriptions relating to figures 3 and 10; figure 3 and 10 paragraph [00141] -----	1-12
	-/--	

[X] Further documents are listed in the continuation of Box C.

[X] 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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 August 2018	16/08/2018

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Cecchini, Stefano

1

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/036412

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/118360 A1 (GENO LLC [US]; FINE DAVID H [US]; ROUNBEHLER DAVID R [US]; VASQUEZ GRE) 2 October 2008 (2008-10-02) passages of the descriptions relating to figure 7; figure 7	1,4
X	WO 2011/094684 A1 (GENO LLC [US]; FINE DAVID H [US]; DENTON RYAN [US]; VASQUEZ GREGORY [U) 4 August 2011 (2011-08-04) figure 1 paragraph [0021] - paragraph [0025]	1-12
X	US 2016/121071 A1 (MOON WILLIAM [US] ET AL) 5 May 2016 (2016-05-05) passages of the descriptions relating to figure 1; figure 1	1,4
A	WO 2014/059405 A1 (INOVA LABS INC [US]) 17 April 2014 (2014-04-17) figure 2 page 13, line 25 - page 14, line 3	4
A	EP 2 832 393 A1 (TEIJIN PHARMA LTD [JP]) 4 February 2015 (2015-02-04) figure 1 paragraph [0026]	4
Y	MOYA M P ET AL: "Inhaled ethyl nitrite gas for persistent pulmonary hypertension of the newborn", LANCET, ELSEVIER, AMSTERDAM, NL, vol. 360, no. 9327, 13 July 2002 (2002-07-13), pages 141-143, XP004798334, ISSN: 0140-6736, DOI: 10.1016/S0140-6736(02)09385-6 the whole document	13

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2018/036412

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011063335 A1	26-05-2011	AU 2010321707 A1	31-05-2012
		CA 2781295 A1	26-05-2011
		EP 2501427 A1	26-09-2012
		JP 5995724 B2	21-09-2016
		JP 2013511360 A	04-04-2013
		US 2011220103 A1	15-09-2011
		US 2014144436 A1	29-05-2014
		WO 2011063335 A1	26-05-2011
WO 2012075420 A1	07-06-2012	AU 2011336358 A1	27-06-2013
		CA 2819854 A1	07-06-2012
		EP 2645860 A1	09-10-2013
		EP 3360557 A2	15-08-2018
		JP 2014506872 A	20-03-2014
		JP 2017061513 A	30-03-2017
		WO 2012075420 A1	07-06-2012
WO 2008118360 A1	02-10-2008	AU 2008232413 A1	02-10-2008
		CA 2681308 A1	02-10-2008
		EP 2131903 A1	16-12-2009
		JP 5575489 B2	20-08-2014
		JP 5950965 B2	13-07-2016
		JP 2010522130 A	01-07-2010
		JP 2015013118 A	22-01-2015
		US 2008317874 A1	25-12-2008
		US 2011240020 A1	06-10-2011
		WO 2008118360 A1	02-10-2008
WO 2011094684 A1	04-08-2011	AU 2011210543 A1	23-08-2012
		CA 2788582 A1	04-08-2011
		EP 2531249 A1	12-12-2012
		JP 5965845 B2	10-08-2016
		JP 2013518615 A	23-05-2013
		US 2011240019 A1	06-10-2011
		WO 2011094684 A1	04-08-2011
US 2016121071 A1	05-05-2016	US 2016121071 A1	05-05-2016
		US 2018126111 A1	10-05-2018
WO 2014059405 A1	17-04-2014	AU 2013328912 A1	07-05-2015
		AU 2018200242 A1	01-02-2018
		BR 112015008203 A2	04-07-2017
		EP 2906278 A1	19-08-2015
		JP 6321663 B2	09-05-2018
		JP 2015531308 A	02-11-2015
		NZ 707064 A	24-11-2017
		US 2014137859 A1	22-05-2014
		US 2016375215 A1	29-12-2016
		WO 2014059405 A1	17-04-2014
EP 2832393 A1	04-02-2015	CN 104220121 A	17-12-2014
		EP 2832393 A1	04-02-2015
		ES 2647283 T3	20-12-2017
		HK 1200748 A1	14-08-2015
		HK 1204588 A1	27-11-2015
		JP 5856287 B2	09-02-2016
		JP WO2013147283 A1	14-12-2015
		KR 20140140015 A	08-12-2014

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2018/036412

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		SG 11201404311X A	30-10-2014
		TW 201345576 A	16-11-2013
		US 2015059741 A1	05-03-2015
		WO 2013147283 A1	03-10-2013

Continuation of Box II.2

Claims Nos.: 14-20

Claims 14-20 define a method of delivering a vaporized agent to a subject, the method comprising the step of flowing the agent and the air mixture out of the device of the invention to be delivered to a subject. This step is explicitly a therapeutic step and thereby the nature of the whole method is rendered therapeutic. Thus, the subject-matter of claims 14-20 is regarded as a method for treatment of the human or animal body by therapy (Rule 39.1 (iv) PCT).
Consequently, the subject-matter of claims 14-20 has not been searched and will not be examined (Rule 66.1(e) PCT, Rule 67.1(iv) PCT).

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guidelines C-IV, 7.2), should the problems which led to the Article 17(2) declaration be overcome.