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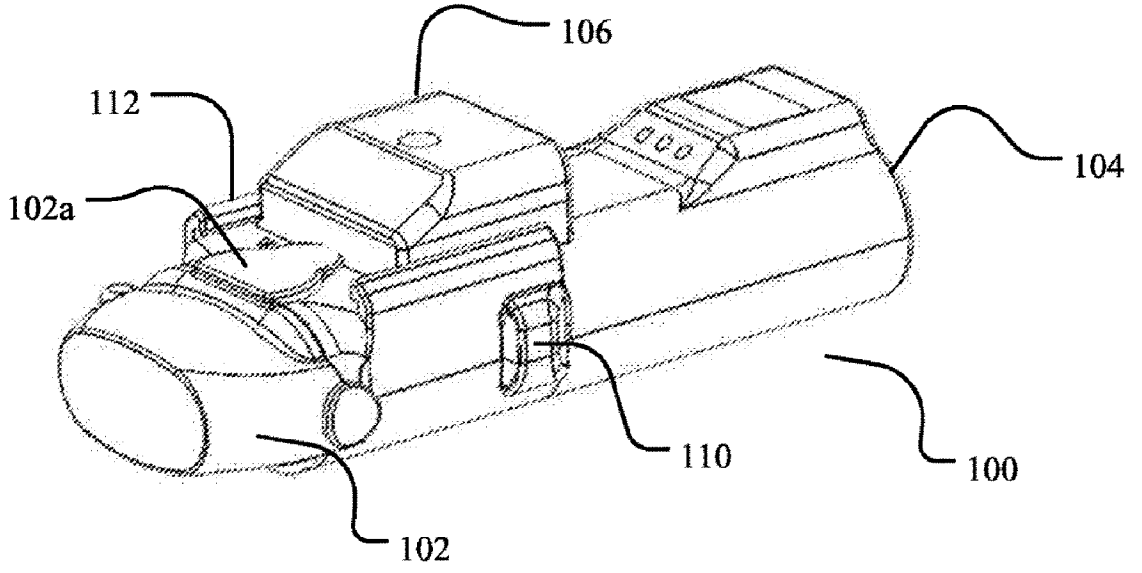
(54) Titre : TRAITEMENT DE CANCERS PULMONAIRES A L'AIDE D'UN DISPOSITIF ELECTRONIQUE D'ADMINISTRATION DE GOUTTELETTES ACTIONNE PAR LA RESPIRATION

(54) Title: TREATMENT OF PULMONARY CANCERS USING AN ELECTRONIC BREATH ACTUATED DROPLET DELIVERY DEVICE

FIG. 1A



(57) Abrégé/Abstract:
Methods for the treatment of pulmonary cancers (primary, secondary, metastatic, etc.) using an electronic breath actuated droplet delivery device to deliver a cancer therapeutic directly to the pulmonary system of a subject in need thereof is disclosed. An in-line droplet delivery device and related methods for delivering precise and repeatable dosages to a subject for pulmonary use is disclosed. The in-line droplet delivery device includes a housing, an ejector mechanism, and at least one differential pressure sensor. The in-line droplet delivery device is automatically breath actuated by the user when the differential pressure sensor senses a predetermined pressure change within housing. The in-line droplet delivery device is then actuated to generate a plume of droplets having an average ejected particle diameter within the respirable size range, e.g, less than about 5-6 µm, so as to target the pulmonary system of the user.

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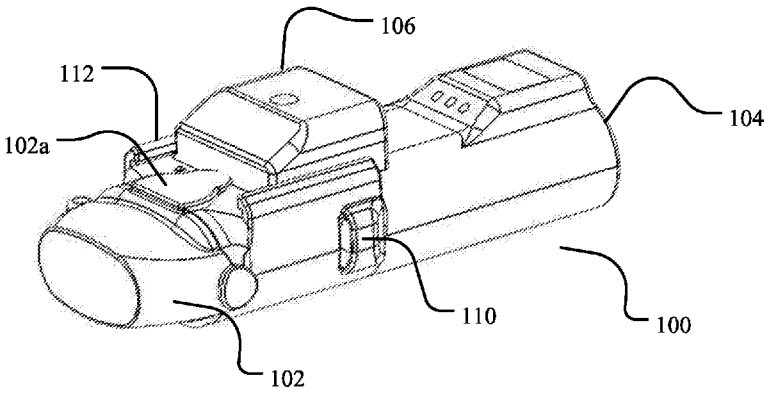
(54) **Title:** TREATMENT OF PULMONARY CANCERS USING AN ELECTRONIC BREATH ACTUATED DROPLET DELIVERY DEVICE

FIG. 1A



(57) **Abstract:** Methods for the treatment of pulmonary cancers (primary, secondary, metastatic, etc.) using an electronic breath actuated droplet delivery device to deliver a cancer therapeutic directly to the pulmonary system of a subject in need thereof is disclosed. An in-line droplet delivery device and related methods for delivering precise and repeatable dosages to a subject for pulmonary use is disclosed. The in-line droplet delivery device includes a housing, an ejector mechanism, and at least one differential pressure sensor. The in-line droplet delivery device is automatically breath actuated by the user when the differential pressure sensor senses a predetermined pressure change within housing. The in-line droplet delivery device is then actuated to generate a plume of droplets having an average ejected particle diameter within the respirable size range, e.g, less than about 5-6 μm, so as to target the pulmonary system of the user.

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TREATMENT OF PULMONARY CANCERS USING AN ELECTRONIC BREATH ACTUATED DROPLET DELIVERY DEVICE

RELATED APPLICATIONS

[0001] The present application claims benefit under 35 U.S.C. § 119 of U.S. Provisional Patent Application No. 62/614,858, filed January 8, 2018, entitled "TREATMENT OF PULMONARY CANCERS USING AN ELECTRONIC BREATH ACTUATED DROPLET DELIVERY DEVICE", and U.S. Provisional Patent Application No. 62/621,957, filed January 25, 2018, entitled "TREATMENT OF PULMONARY CANCERS USING AN ELECTRONIC BREATH ACTUATED DROPLET DELIVERY DEVICE", the contents of which are each herein incorporated by reference in their entireties.

FIELD OF THE INVENTION

[0002] This disclosure relates to methods for the treatment of pulmonary cancers using droplet delivery devices and more specifically to droplet delivery devices for the delivery of fluids to the pulmonary system.

BACKGROUND OF THE INVENTION

[0003] Lung cancer is the leading cause of cancer death in the United States killing an estimated 160,000 people annually with approximately 200,000 newly diagnosed in 2010 alone. The number of deaths caused by lung cancer exceeds that of colon, breast and prostate cancer combined. Lung cancer is associated with a dismal 5-year survival rate of 15% due to the fact that the majority of patients are diagnosed in the late stages of disease after metastasis has occurred. Human lung cancer is comprised of two main histopathologic groups, non-small cell (NSCLC) and small cell lung cancer (SCLC). Approximately 80% of lung cancers are NSCLC, originating from lung epithelial cells. NSCLC is further subdivided into adeno, squamous, and large cell subtypes. Adenocarcinomas arise in the periphery and comprise ~40% of all NSCLC.

[0004] While many treatments have been proposed for lung cancer, it would be desirable to develop improved treatments with reduced side effects.

SUMMARY OF THE INVENTION

[0005] In one aspect, this disclosure relates to a method for treating pulmonary cancer in a subject in need thereof by delivering a therapeutic agent as an ejected stream of droplets in a respirable range to the pulmonary system of t. The method may comprise: (a) generating an ejected stream of droplets via a breath actuated droplet delivery device of the disclosure,

wherein at least about 50% of the ejected stream of droplets have an average ejected droplet diameter of less than about 6 μm; and (b) delivering the ejected stream of droplets to the pulmonary system of the subject such that at least about 50% of the mass of the ejected stream of droplets is delivered in a respirable range to the pulmonary system of a subject during use to thereby treat the pulmonary cancer.

[0006] In certain embodiments, the pulmonary cancer may be a primary, secondary or metastatic pulmonary cancer. In other embodiments, the pulmonary cancer may be non-small cell lung cancer (NSCLC) or small cell lunch cancer (SCLC). The therapeutic agent may comprise a cancer therapeutic selected from chemotherapeutic agents, immune checkpoint inhibitors, other antibody and immune stimulating therapeutics, and various combinations thereof. In yet other aspects, the therapeutic agent may be delivered to the pulmonary system of the subject at higher concentrations, as compared to oral, systemic, or parenteral administration.

[0007] In certain embodiments, the droplet delivery device of the disclosure is configured in an in-line orientation in that the housing, its internal components, and various device components (e.g., the mouthpiece, air inlet flow element, etc.) are orientated in a substantially in-line or parallel configuration (e.g., along the airflow path) so as to form a small, hand-held device.

[0008] In certain embodiments, the droplet delivery device may include: a housing; a mouthpiece positioned at the airflow exit side of the housing; a reservoir disposed within or in fluid communication with the housing for receiving a volume of fluid; an ejector mechanism in fluid communication with the reservoir, the ejector mechanism comprising a piezoelectric actuator and an aperture plate, the aperture plate having a plurality of openings formed through its thickness and the piezoelectric actuator operable to oscillate the aperture plate at a frequency to thereby generate an ejected stream of droplets, at least one differential pressure sensor positioned within the housing; the at least one differential pressure sensor configured to activate the ejector mechanism upon sensing a pre-determined pressure change within the mouthpiece to thereby generate an ejected stream of droplets; the ejector mechanism configured to generate the ejected stream of droplets wherein at least about 50% of the droplets have an average ejected droplet diameter of less than about 6 microns, such that at least about 50% of the mass of the ejected stream of droplets is delivered in a respirable range to the pulmonary system of a subject during use.

[0009] In some aspects, the droplet delivery device further includes an air inlet flow element positioned in the airflow at the airflow entrance of the device and configured to

facilitate non-turbulent (i.e., laminar and/or transitional) airflow across the exit side of aperture plate and to provide sufficient airflow to ensure that the ejected stream of droplets flows through the droplet delivery device during use. In some embodiments, the air inlet flow element may be positioned within the mouthpiece.

[0010] In certain embodiments, the housing and ejector mechanism are oriented such that the exit side of the aperture plate is perpendicular to the direction of airflow and the stream of droplets is ejected in parallel to the direction of airflow. In other embodiments, the housing and ejector mechanism are oriented such that the exit side of the aperture plate is parallel to the direction of airflow and the stream of droplets is ejected substantially perpendicularly to the direction of airflow such that the ejected stream of droplets is directed through the housing at an approximate 90 degree change of trajectory prior to expulsion from the housing.

[0011] In certain aspects, the droplet delivery device further includes a surface tension plate between the aperture plate and the reservoir, wherein the surface tension plate is configured to increase contact between the volume of fluid and the aperture plate. In other aspects, the ejector mechanism and the surface tension plate are configured in parallel orientation. In yet other aspects, the surface tension plate is located within 2 mm of the aperture plate so as to create sufficient hydrostatic force to provide capillary flow between the surface tension plate and the aperture plate.

[0012] In yet other aspects, the aperture plate of the droplet delivery device comprises a domed shape. In other aspects, the aperture plate may be formed of a metal, e.g., stainless steel, nickel, cobalt, titanium, iridium, platinum, or palladium or alloys thereof. Alternatively, the aperture plate can be formed of suitable material, including other metals or polymers. In certain embodiments, the aperture plate is comprised of, e.g., poly ether ether ketone (PEEK), polyimide, polyetherimide, polyvinylidine fluoride (PVDF), ultra-high molecular weight polyethylene (UHMWPE), nickel, nickel-cobalt, palladium, nickel-palladium, platinum, or other suitable metal alloys, and combinations thereof. In other aspects, one or more of the plurality of openings of the aperture plate have different cross-sectional shapes or diameters to thereby provide ejected droplets having different average ejected droplet diameters.

[0013] In yet other aspects, the reservoir of the droplet delivery device is removably coupled with the housing. In other aspects, the reservoir of the droplet delivery device is coupled to the ejector mechanism to form a combination reservoir/ejector mechanism module, and the combination reservoir/ejector mechanism module is removably coupled with the housing.

[0014] In other aspects, the droplet delivery device may further include a wireless communication module. In some aspects, the wireless communication module is a Bluetooth transmitter.

[0015] In yet other aspects, the droplet delivery device may further include one or more sensors selected from an infer-red transmitter, a photodetector, an additional pressure sensor, and combinations thereof.

[0016] In one aspect, the disclosure relates to a method for generating and delivering a fluid as an ejected stream of droplets to the pulmonary system of a subject in a respirable range. The method may comprise: (a) generating an ejected stream of droplets via a breath actuated droplet delivery device of the disclosure, wherein at least about 50% of the ejected stream of droplets have an average ejected droplet diameter of less than about 6 μm; and (b) delivering the ejected stream of droplets to the pulmonary system of the subject such that at least about 50% of the mass of the ejected stream of droplets is delivered in a respirable range to the pulmonary system of a subject during use.

[0017] While multiple embodiments are disclosed, still other embodiments of the present disclosure will become apparent to those skilled in the art from the following detailed description, which shows and describes illustrative embodiments of the disclosure. As will be realized, the invention is capable of modifications in various aspects, all without departing from the spirit and scope of the present disclosure. Accordingly, the detailed descriptions are to be regarded as illustrative in nature and not restrictive.

BRIEF DESCRIPTION OF THE DRAWINGS

[0018] **FIGS. 1A-1B** illustrate perspective views of an exemplary in-line droplet delivery device, in accordance with embodiments of the disclosure.

[0019] **FIG. 2** is an exploded view of an in-line droplet delivery device of **FIG. 1A-1B**, in accordance with embodiments of the disclosure..

[0020] **FIG. 3A-1** is a partial perspective view of a base unit of an in-line droplet delivery device of **FIG. 1A-1B**, in accordance with embodiments of the disclosure.

[0021] **FIG. 3A-2** is an exploded view of an in-line droplet delivery device of **FIG. 1A-1B**, in accordance with embodiments of the disclosure.

[0022] **FIG. 3B-1** is a bottom perspective view of a drug delivery ampoule of an in-line droplet delivery device of **FIG. 1A-1B**, in accordance with embodiments of the disclosure.

[0023] **FIG. 3B-2** is an exploded view of an in-line droplet delivery device of **FIG. 1A-1B**, in accordance with embodiments of the disclosure.

[0024] **FIGS. 3C-1, 3C-2,** and **3C-3** are cross section perspective views of an in-line droplet delivery device of **FIG. 1A-1B**, in accordance with embodiments of the disclosure.

[0025] **FIGS. 4A-4B** illustrate perspective views of another exemplary in-line droplet delivery device, in accordance with embodiments of the disclosure.

[0026] **FIG. 5** is an exploded view of an in-line droplet delivery device of **FIG. 4A-4B**, in accordance with embodiments of the disclosure.

[0027] **FIG. 6** is a cross section perspective view of an in-line droplet delivery device of **FIG. 4A-4B**, in accordance with embodiments of the disclosure.

[0028] **FIG. 7** is a perspective view of an in-line droplet delivery device of **FIG. 4A-4B** without the drug delivery ampoule inserted, in accordance with embodiments of the disclosure.

[0029] **FIGS. 8A-8B** are perspective views of a drug delivery ampoule and mouthpiece cover, showing a front view (**FIG. 8A**) and back view (**FIG. 8B**), in accordance with embodiments of the disclosure.

[0030] **FIGS. 9A-9D** show alternative drug delivery ampoules. **FIG. 9A** shows a perspective view of a first embodiment of a drug delivery ampoule, with **FIG. 9B** showing a top exploded view and **FIG. 9C** showing a bottom exploded view of the ampoule of **FIG. 9A**. FIG. 9A illustrates a cross-section of an alternative embodiment of drug delivery ampoule, in accordance with embodiments of the disclosure.

[0031] **FIG. 10A** is a partial cross section perspective view of an in-line droplet delivery device of **FIG. 1A-1B** comprising a drug delivery ampoule, mouthpiece including an air inlet flow element, and mouthpiece cover, in accordance with an embodiment of the disclosure.

[0032] **FIG. 10B** is a front view of an in-line droplet delivery device of **FIG. 1A-1B** comprising a drug delivery ampoule and mouthpiece including an air inlet flow element, in accordance with an embodiment of the disclosure.

[0033] **FIG. 10C** is a exploded view of components of an in-line droplet delivery device of **FIG. 1A-1B** including a mouthpiece and internal housing, in accordance with an embodiment of the disclosure.

[0034] **FIG. 11A** is a plot of the differential pressure as a function of flow rates through exemplary air inlet flow elements as a function of number of holes, in accordance with an embodiment of the disclosure.

[0035] **FIG. 11B** is a plot of the differential pressure as a function of flow rates through exemplary air inlet flow elements as a function of screen hole size and number of holes set at a constant, 17 holes, in accordance with an embodiment of the disclosure..

[0036] **FIG. 12A** shows an exemplary drug delivery ampoule with a mouthpiece interfaced at the airflow exit side of the device, in accordance with an embodiment of the disclosure. **FIG. 12B** shows a front cross-section and **FIG. 12C** shows a side cross-section, with **FIG. 12D** showing the same views with exemplary dimensions.

[0037] **FIG. 13A** shows an alternative drug delivery ampoule with a mouthpiece interfaced at the airflow exit side of the device, in accordance with an embodiment of the disclosure. **FIG. 13B** shows a front cross-section and **FIG. 13C** shows a side cross-section, with **FIG. 13D** showing the same views with exemplary dimensions.

[0038] **FIG. 14A** shows an alternative drug delivery ampoule with a mouthpiece interfaced at the airflow exit side of the device, in accordance with an embodiment of the disclosure. **FIG. 14B** shows a front cross-section and **FIG. 14C** shows a side cross-section, with **FIG. 14D** showing the same views with exemplary dimensions.

[0039] **FIG. 15A** shows an exemplary drug delivery ampoule with a mouthpiece interfaced at the airflow exit side of the device, in accordance with an embodiment of the disclosure. The mouthpiece includes two airflow entrances on the exterior sides of the mouthpiece, and two interior baffles with additional airflow entrances to provide resistance and modeling of airflow. **FIG. 15B** shows a front cross-section and **FIG. 15C** shows a side cross-section, with **FIG. 15D** showing the same views with exemplary dimensions.

[0040] **FIG. 16A** shows an exemplary drug delivery ampoule with a mouthpiece interfaced at the airflow exit side of the device, in accordance with an embodiment of the disclosure. The mouthpiece includes two airflow entrances on the exterior sides of the mouthpiece, and two interior baffles with additional airflow entrances to provide resistance and modeling of airflow. **FIG. 16B** shows a front cross-section and **FIG. 16C** shows a side cross-section, with **FIG. 16D** showing the same views with exemplary dimensions.

[0041] **FIG. 17A** shows an exemplary drug delivery ampoule with a mouthpiece interfaced at the airflow exit side of the device, in accordance with an embodiment of the disclosure. The mouthpiece includes two airflow entrances on the exterior sides of the mouthpiece, and a substantially concentric baffle (two arcs that form a circle with the top and bottom of the mouthpiece) with two additional airflow entrances to provide resistance and modeling of airflow. **FIG. 17B** shows a front cross-section and **FIG. 17C** shows a side cross-section, with **FIG. 17D** showing the same views with exemplary dimensions.

[0042] **FIG. 18A** shows an exemplary drug delivery ampoule with a mouthpiece interfaced at the airflow exit side of the device, in accordance with an embodiment of the disclosure. The mouthpiece includes two airflow entrances on the exterior sides of the mouthpiece, and a substantially concentric baffle (two arcs that form a circle with the top and bottom of the mouthpiece) with four airflow entrances to provide resistance and modeling of airflow. **FIG. 18B** shows a front cross-section and **FIG. 18C** shows a side cross-section, with **FIG. 18D** showing the same views with exemplary dimensions.

[0043] **FIG. 19A** shows an exemplary drug delivery ampoule with a mouthpiece interfaced at the airflow exit side of the device, in accordance with an embodiment of the disclosure. The mouthpiece includes two airflow entrances on the exterior sides of the mouthpiece, and a substantially concentric baffle with two additional airflow entrances to provide resistance and modeling of airflow. In addition, the interior area of the mouthpiece between the concentric baffle and the wall of the mouthpiece includes an array element positioned above the airflow entrances to provide additional resistance and modeling to airflow. The array element is positioned in a parallel arrangement with the direction of airflow. **FIG. 19B** shows a front cross-section and **FIG. 1919C** shows a side cross-section, with **FIG. 19D** showing the same views with exemplary dimensions.

[0044] **FIG. 20** is a plot of spray efficiency as a function of flow rates through exemplary air inlet flow elements as a function of number and configuration of openings, baffles, etc., in accordance with an embodiment of the disclosure.

[0045] **FIGS. 21A-21D** illustrate exemplary aperture plate seal mechanisms, in accordance with embodiments of the disclosure. **FIG. 21A** showing the ampoule in end view, **FIG. 21B** and **FIG. 21C** showing the ampoule in side view. **FIG. 21D** illustrates an alternative embodiment wherein the mouthpiece cover includes an aperture plate plug.

[0046] **FIGS. 22A-22G** show photomicrographs to illustrate location of deposits of hIgG delivered to the pulmonary system via delivery devices of the disclosure. **FIG. 22A** shows an annotated photomicrograph of test subject rat 2.1; **FIG. 22B** shows the distal alveoli of test subject rat 2.1; **FIG. 22C** shows the proximal bronchiole of test subject rat 2.1; **FIG. 22D** shows the distal alveoli of test subject rat 3.1; **FIG. 22E** shows the distal bronchiole of test subject rat 3.1; **FIG. 22F** shows the distal alveoli of test subject rat 4.2; and **FIG. 22G** shows the distal bronchiole of test subject rat 4.2.

DETAILED DESCRIPTION

[0047] Certain aspects of the disclosure relate to methods for the treatment of pulmonary cancers (primary, secondary, metastatic, etc.) using an electronic breath actuated droplet delivery device to deliver a therapeutic agent directly to the pulmonary system of a subject in need thereof.

[0048] Effective delivery of medication to the deep pulmonary regions of the lungs through the alveoli, has always posed a problem, especially to children and elderly, as well as to those with the diseased state, owing to their limited lung capacity and constriction of the breathing passageways. The impact of constricted lung passageways limits deep inspiration and synchronization of the administered dose with the inspiration/expiration cycle. For optimum deposition in alveolar airways, droplets with aerodynamic diameters in the ranges of 1 to 5 μm are optimal, with droplets below about 4 μm shown to more effectively reach the alveolar region of the lungs, while larger droplets above about 6 μm are deposited on the tongue or strike the throat and coat the bronchial passages. Smaller droplets, for example less than about 1 μm that penetrate more deeply into the lungs have a tendency to be exhaled.

[0049] Certain aspects of the disclosure relate to an electronic, fully digital platform for delivery of inhaled therapeutics, described herein as an in-line droplet delivery device or soft mist inhaler (SMI) device. The device provides substantial improvements over current inhaled delivery systems by improving dosing precision, dosing reliability, and delivery to the patient. In certain embodiments, the device of the disclosure includes fully integrated monitoring capabilities designed to enhance compliance and ultimately reduce disease associated morbidity.

[0050] In certain aspects of the disclosure, an in-line droplet delivery device, or soft mist inhaler (SMI) device (these terms are used interchangeably herein) is disclosed. The SMI is a novel inhaled drug delivery device that overcomes limitations of the currently available pulmonary drug delivery devices.

[0051] In certain aspects, the present disclosure relates to an in-line droplet delivery device for delivery a fluid as an ejected stream of droplets to the pulmonary system of a subject and related methods of delivering safe, suitable, and repeatable dosages to the pulmonary system of a subject. The present disclosure also includes an in-line droplet delivery device and system capable of delivering a defined volume of fluid in the form of an ejected stream of droplets such that an adequate and repeatable high percentage of the droplets are delivered into the desired location within the airways, e.g., the alveolar airways of the subject during use.

[0052] The present disclosure provides an in-line droplet delivery device for delivery of a fluid as an ejected stream of droplets to the pulmonary system of a subject, the device comprising a housing, a mouthpiece, a reservoir for receiving a volume of fluid, and an ejector mechanism including a piezoelectric actuator and an aperture plate, wherein the ejector mechanism is configured to eject a stream of droplets having an average ejected droplet diameter of less than about 6 microns, preferably less than about 5 microns.

[0053] As shown in further detail herein, the droplet delivery device is configured in an in-line orientation in that the housing, its internal components, and various device components (e.g., the mouthpiece, air inlet flow element, etc.) are orientated in a substantially in-line or parallel configuration (e.g., along the airflow path) so as to form a small, hand-held device. In certain embodiments, the housing and ejector mechanism are oriented such that the exit side of aperture plate is perpendicular to the direction of airflow and the stream of droplets is ejected in parallel to the direction of airflow. In other embodiments, the housing and ejector mechanism are oriented such that the exit side of aperture plate is parallel to the direction of airflow and the stream of droplets is ejected substantially perpendicularly to the direction of airflow such that the ejected stream of droplets is directed through the housing at an approximate 90 degree change of trajectory prior to expulsion from the housing.

[0054] In specific embodiments, the ejector mechanism is electronically breath activated by at least one differential pressure sensor located within the housing of the in-line droplet delivery device upon sensing a pre-determined pressure change within the mouthpiece. In certain embodiments, such a pre-determined pressure change may be sensed during an inspiration cycle by a user of the device, as will be explained in further detail herein.

[0055] In some aspects, the droplet delivery device further includes an air inlet flow element positioned in the airflow at the airflow entrance of the housing and configured to facilitate non-turbulent (i.e., laminar and/or transitional) airflow across the exit side of aperture plate and to provide sufficient airflow to ensure that the ejected stream of droplets flows through the droplet delivery device during use. In some embodiments, the air inlet flow element may be positioned within the mouthpiece As will be described in further detail herein, the air inlet flow element may be positioned behind the exit side of the aperture plate along the direction of airflow, or in-line or in front of the exit side of the aperture plate along the direction of airflow. In certain embodiments, the air inlet flow element comprises one or more openings formed there through and configured to increase or decrease internal pressure resistance within the droplet delivery device during use. For instance, the air inlet flow

element comprises an array of one or openings. In the embodiments, the air inlet flow element comprises one or more baffles, e.g., wherein the one or more baffles comprise one or more airflow openings.

[0056] In accordance with certain aspects of the disclosure, effective deposition into the lungs generally requires droplets less than about 5-6 μm in diameter. Without intending to be limited by theory, to deliver fluid to the lungs a droplet delivery device must impart a momentum that is sufficiently high to permit ejection out of the device, but sufficiently low to prevent deposition on the tongue or in the back of the throat. Droplets below approximately 5-6 μm in diameter are transported almost completely by motion of the airstream and entrained air that carry them and not by their own momentum.

[0057] In certain aspects, the present disclosure includes and provides an ejector mechanism configured to eject a stream of droplets within the respirable range of less than about 5-6 μm, preferably less than about 5 μm. The ejector mechanism is comprised of an aperture plate that is directly or indirectly coupled to a piezoelectric actuator. In certain implementations, the aperture plate may be coupled to an actuator plate that is coupled to the piezoelectric actuator. The aperture plate generally includes a plurality of openings formed through its thickness and the piezoelectric actuator directly or indirectly (e.g. via an actuator plate) oscillates the aperture plate, having fluid in contact with one surface of the aperture plate, at a frequency and voltage to generate a directed aerosol stream of droplets through the openings of the aperture plate into the lungs, as the patient inhales. In other implementations where the aperture plate is coupled to the actuator plate, the actuator plate is oscillated by the piezoelectric oscillator at a frequency and voltage to generate a directed aerosol stream or plume of aerosol droplets.

[0058] In certain aspects, the present disclosure relates to an in-line droplet delivery device for delivering a fluid as an ejected stream of droplets to the pulmonary system of a subject. The ejected stream of droplets includes, without limitation, droplets formed from solutions, suspensions or emulsions which have viscosities in a range capable of droplet formation using the ejector mechanism. In certain aspects, the therapeutic agents may be delivered at a high dose concentration and efficacy, as compared to alternative dosing routes and standard inhalation technologies.

[0059] In certain embodiments, the in-line droplet delivery device may be used to deliver therapeutic agents for the treatment or prevention of pulmonary cancer. In certain aspects, the cancer therapeutics include small molecules, therapeutic peptides, proteins, antibodies, and other bioengineered molecules, which may be administered to the pulmonary

system of a subject for both local and/or systemic treatment or prevention of a pulmonary cancer (primary, secondary, metastatic, etc.).

[0060] In certain embodiments, the cancer therapeutic may be comprised of the active agent, a carrier, and other suitable pharmaceutically acceptable excipients. For instance, various carriers may include colloidal dispersions, microparticles, nanoparticles, polyketal microparticles and nanoparticles, liposomes, polymer conjugates, protein or nucleic acid conjugates, dendrimers, nanostructured lipid carriers (NLC), nanospheres, and various combinations thereof.

[0061] In certain embodiments, the active agent of the cancer therapeutic may be selected from chemotherapeutic agents, immune checkpoint inhibitors, and other antibody and immune stimulating therapeutics, and various combinations thereof.

[0062] Exemplary chemotherapeutic agents include paclitaxel, doxorubicin, gemcitabine, 9-nitrocamptothecin, 5-azacytidine, celecoxib, 5-fluorouracil, cisplatin, carboplatin, oxaliplatin, nedaplatin, picoplatin, and other known chemotherapy agents.

[0063] Exemplary immune checkpoint inhibitors include CTLA-4, PD-1 and PD-L1 inhibitors, such as Pembrolizumab (Keytruda), Nivolumab (Opdivo), Atezolizumab (Tecentriq), Avelumab (Bavencio), Durvalumab (Imfinzi), and Ipilimumab (Yervoy). In other aspects, various targeted monoclonal antibodies may be used, e.g., Bevacizumab (Avastin), Ramucirumab (Cyramza), or Necitumumab (Portrazza).

[0064] Other immune stimulating therapeutics may include synthetic oligonucleotides that activate Toll-like receptors (TLRs), such as CpG oligonucleotides that activate TLR9.

[0065] In certain embodiments, combinations of one or more chemotherapeutic agents, e.g., platinum based chemotherapeutic agents or other chemotherapy agent together, to PD-1, e.g., nivolumab, and/or CTLA-4, ipilimumab, inhibitors may be used. For instance, cisplatin, docetaxel, or doxorubicin alone or in combination with one or more immune checkpoint inhibitors or other therapeutic agents may be used in connection with the methods of the disclosure.

[0066] By way of non-limiting example, therapeutic agents which may be delivered via the pulmonary system for the treatment or prevention of pulmonary cancer include one or more of the following:

	Compound
Chemotherapeutic Drugs	Paclitaxel
	Doxorubicin
	Gemcitabine
	9-Nitrocamptothecin
	5-Azacytidine
	Celecoxib (+ systemic docetaxel)
	5-Fluorouracil
	Cisplatin
Immunotherapeutic Agents	IL-2
	IL-2 (+ NK cell infusion)
	GM-CSF
	CpG-ODN
	LPS
Monoclonal Antibodies	Cetuximab
	Cetuximab + AvidinOX
Genes	PEI–p53
	PEI-IL-12
	PEI–PTEN
	BC-819
	rAAV-M3-4E-BP1
	DNA/Beclin1
	PEI-p53 + 9NC-DLPC
	Adenoviral-type 5 with human ABCA10 transgene + cisplatin
Antisense Oligonucleotides, siRNA, shRNA	Akt1 siRNA
	PEI-WT1 RNAi
	Small hairpin osteopontin
	MRP1 and BCL2 ASO

[0067] Certain benefits of the pulmonary route for delivery of drugs and other medications include a non-invasive, needle-free delivery system that is suitable for delivery of a wide range of substances from small molecules to very large proteins, reduced level of metabolizing enzymes compared to the GI tract, and absorbed molecules do not undergo a first pass liver effect. (A. Tronde, et al., J Pharm Sci, 92 (2003) 1216-1233; A.L. Adjei, et al., Inhalation Delivery of Therapeutic Peptides and Proteins, M. Dekker, New York, 1997). Further, for local pulmonary indications, medications that are administered orally or parenterally (IM, SC, IV, IP, etc.) are diluted through the body, while medications given directly into the lungs may provide concentrations at the target site (the lungs) that are about

100 times higher than the same parenteral dose. As such, in accordance with certain aspects of the disclosure, lower dosages may be administered to a subject via inhalation for local delivery to the lungs, as compared to equivalently effective parenterally administered dosages. Such lower dosages may have the added benefit of reducing side effects of the active agent, e.g., due to reduced local and/or systemic exposure.

[0068] Another benefit of giving medication directly into the lungs is that systemic side effects can be minimized, e.g., as compared to oral, systemic, or parenteral administration.

[0069] In certain aspects, in accordance with the present disclosure, it has been found that exemplary antibody compositions (hIgG) can be successfully delivered in a dose dependent manner to the lungs of a subject via inhalation using a device of the disclosure, and can be distributed in proximal and distal lung tissues, including alveoli, bronchioles, and trachea (see Examples). In addition, it has been found that exemplary antibody compositions (hIgG) can be successfully delivered locally to the lungs via inhalation using a device of the disclosure in a manner that minimizes systemic uptake.

[0070] In this regard, in accordance with aspects of the disclosure, substantially larger dosages of active agent can be locally delivered to the lungs via inhalation in a manner that results in minimal systemic exposure to and uptake of the active agent. For instance, similar systemic plasma concentrations of an exemplary antibody are observed in subjects when dosed via inhalation at a dosage amount 250 times greater than when dosed via oral, systemic or parenteral route (see Examples).

[0071] As discussed above, effective delivery of droplets deep into the lung airways require droplets that are less than about 5-6 microns in diameter, specifically droplets with mass mean aerodynamic diameters (MMAD) that are less than about 5 microns. The mass mean aerodynamic diameter is defined as the diameter at which 50% of the droplets by mass are larger and 50% are smaller. In certain aspects of the disclosure, in order to deposit in the alveolar airways, droplets in this size range must have momentum that is sufficiently high to permit ejection out of the device, but sufficiently low to overcome deposition onto the tongue (soft palate) or pharynx.

[0072] In other aspects of the disclosure, methods for generating an ejected stream of droplets for delivery to the pulmonary system of user using the droplet delivery devices of the disclosure are provided. In certain embodiments, the ejected stream of droplets is generated in a controllable and defined droplet size range. By way of example, the droplet size range includes at least about 50%, at least about 60%, at least about 70%, at least about 85%, at

least about 90%, between about 50% and about 90%, between about 60% and about 90%, between about 70% and about 90%, etc., of the ejected droplets are in the respirable range of below about 5 μm.

[0073] In other embodiments, the ejected stream of droplets may have one or more diameters, such that droplets having multiple diameters are generated so as to target multiple regions in the airways (mouth, tongue, throat, upper airways, lower airways, deep lung, etc.) By way of example, droplet diameters may range from about 1 μm to about 200 μm, about 2 μm to about 100 μm, about 2 μm to about 60 μm, about 2 μm to about 40 μm, about 2 μm to about 20 μm, about 1 μm to about 5μm, about 1 μm to about 4.7 μm, about 1 μm to about 4 μm, about 10 μm to about 40 μm, about 10 μm to about 20 μm, about 5 μm to about 10 μm, and combinations thereof. In particular embodiments, at least a fraction of the droplets have diameters in the respirable range, while other droplets may have diameters in other sizes so as to target non-respirable locations (e.g., larger than 5 μm). Illustrative ejected droplet streams in this regard might have 50% - 70% of droplets in the respirable range (less than about 5 μm), and 30% -50% outside of the respirable range (about 5 μm – about 10 μm, about 5 μm – about 20 μm, etc.)

[0074] In another embodiment, methods for delivering safe, suitable, and repeatable dosages of a medicament to the pulmonary system using the droplet delivery devices of the disclosure are provided. The methods deliver an ejected stream of droplets to the desired location within the pulmonary system of the subject, including the deep lungs and alveolar airways.

[0075] Suitable dosage and administration regimen may be determined based on the specific cancer therapeutic or combination of cancer therapeutic agents to be administered to the subject in need thereof. As discussed herein, the present methods and devices allow for delivery of high concentrations of active agent directly to the pulmonary system of a subject. Suitable dosages and dosing regimens may be determined based, at least in part, on lung clearance properties of the therapeutic agent and desired therapeutic concentrations of the therapeutic agent at the site of interest (e.g., tumor site, upper airways, lower airways, etc.). Many factors, including those described herein, can influence the desired dosage. Once the desired dosage is determined, and also if needed, desired frequency, such doses can be delivered. Frequency of dosing can vary by number of times, periodicity or both.

[0076] The term "therapeutically effective" amount refers to an amount of an active agent used to treat, ameliorate, prevent, or eliminate the identified condition (e.g., lung cancer), or to exhibit a detectable therapeutic or preventive effect. The effect can be detected

by, for example, chemical markers, antigen levels, or time to a measurable event, such as morbidity or mortality. The precise effective amount for a subject will depend upon the subject's body weight, size, and health; the nature and extent of the condition; and the therapeutic or combination of therapeutics selected for administration.

[0077] In certain aspects of the disclosure, an in-line droplet delivery device for delivery an ejected stream of droplets to the pulmonary system of a subject is provided. The in-line droplet delivery device generally includes a housing, a mouthpiece positioned at the airflow exit side of the housing, a reservoir disposed in or in fluid communication with the housing for receiving a volume of fluid, an ejector mechanism in fluid communication with the reservoir, and at least one differential pressure sensor positioned within the housing. The housing, its internal components, and various device components (e.g., the mouthpiece, air inlet flow element, etc.) are orientated in a substantially in-line or parallel configuration (e.g., along the airflow path) so as to form a small, hand-held device. The differential pressure sensor is configured to electronically breath activate the ejector mechanism upon sensing a pre-determined pressure change within the mouthpiece, and the ejector mechanism is configured to generate an ejected stream of droplets.

[0078] In certain embodiments, the mouthpiece may be interfaced with (and optionally removable and/or replaceable), integrated into, or part of the housing. In other embodiments, the mouthpiece may be interfaced with (and optionally removable and/or replaceable), integrated into, or part of the drug delivery ampoule.

[0079] The ejector mechanism may include a piezoelectric actuator which is directly or indirectly coupled to an aperture plate having a plurality of openings formed through its thickness. The piezoelectric actuator is operable to directly or indirectly oscillate the aperture plate at a frequency to thereby generate an ejected stream of droplets.

[0080] In certain embodiments, the housing and ejector mechanism are oriented such that the exit side of aperture plate is perpendicular to the direction of airflow and the stream of droplets is ejected in parallel to the direction of airflow. In other embodiments, the housing and ejector mechanism are oriented such that the exit side of aperture plate is parallel to the direction of airflow and the stream of droplets is ejected substantially perpendicularly to the direction of airflow such that the ejected stream of droplets is directed through the housing at an approximate 90 degree change of trajectory prior to expulsion from the housing.

[0081] In certain embodiments, the in-line droplet delivery device is comprised of a separate drug delivery ampoule with an ejector mechanism (e.g., combination

reservoir/ejector mechanism module) embedded within a surface of a drug reservoir, and a handheld base unit (e.g., housing) including a differential pressure sensor, a microprocessor and three AAA batteries. In certain embodiments, the handheld base unit also includes a mouthpiece, optionally removable, an optional mouthpiece cover, and an optional ejector plate seal. The microprocessor controls dose delivery, dose counting and software designed monitoring parameters that can be transmitted through blue-tooth technology. The ejector mechanism optimizes droplet delivery to the lungs by creating an ejected droplet stream in a predefined range with a high degree of accuracy and repeatability. Initial droplet studies show at least 65% to 70% of droplets ejected from the device are in the respirable range (e.g., 1 – 5 μm).

[0082] In certain embodiments, the in-line droplet delivery device may include a combination reservoir/ejector mechanism module (e.g., drug delivery ampoule) that may be replaceable or disposable either on a periodic basis, e.g., a daily, weekly, monthly, as-needed, etc. basis, as may be suitable for a prescription or over-the-counter medication. The reservoir may be prefilled and stored in a pharmacy for dispensing to patients or filled at the pharmacy or elsewhere by using a suitable injection means such as a hollow injection syringe driven manually or driven by a micro-pump. The syringe may fill the reservoir by pumping fluid into or out of a rigid container or other collapsible or non-collapsible reservoir. In certain aspects, such disposable/replaceable, combination reservoir/ejector mechanism module may minimize and prevent buildup of surface deposits or surface microbial contamination on the aperture plate, owing to its short in-use time.

[0083] In other embodiments, the in-line droplet delivery device of the disclosure may include a small volume drug ampoule, e.g., configured as a single use ampoule (e.g., disposable on a daily or on-use basis). Such embodiments are particularly useful with therapeutic agents that are sensitive to storage conditions, e.g., sensitive to degradation, aggregation, conformational changes, contamination, etc. In this regard, the small volume drug ampoule allows for sterile storage of a therapeutic agent under appropriate conditions until the time of use, e.g., under a temperature controlled environment, as a powder-for-reconstitution, etc. By way of non-limiting example, the small volume drug ampoule of the disclosure is particular suitable for use with therapeutic peptides, proteins, antibodies, and other bioengineered molecules or biologics. However, the disclosure is not so limited, and the small volume drug ampoule may be used with any therapeutic agent known in the art.

[0084] Without intending to be limited by theory, in certain aspects, the small volume drug ampoule of the disclosure may offer advantages over larger volume/multi-use ampoules

in that, e.g., the limited duration of use minimizes evaporation of fluid in the reservoir, minimizes the possibility of contamination of fluid in the reservoir and/or the ejector surface, minimizes the duration of time of the ampoule is held at non-controlled storage conditions, etc.

[0085] In certain embodiments, the small volume drug ampoule includes a drug reservoir for receiving a small volume of fluid, e.g., a volume equivalent to 10 or fewer dosages, a volume equivalent to 5 or fewer dosages, a volume equivalent to 4 or fewer dosages, a volume equivalent to 3 or fewer dosages, a volume equivalent to 2 or fewer dosages, a single dose volume. The small volume drug ampoule is configured to facilitate the ejection of small, e.g., single use, volumes of a therapeutic agent.

[0086] In certain embodiments, the small volume drug ampoule may include a reservoir which comprises an internal flexible membrane separating two internal volumes, a first background pressure fluid volume and a second drug volume. In certain aspects, the membrane separates the two volumes such that the background pressure fluid volume creates an area of fluid behind/above the drug volume without allowing mixing or diluting of the therapeutic agent by the background pressure fluid. The small volume drug ampoule may further comprise an air exchange vent or air space in the region of the background pressure fluid volume, configured to prevent or relieve the creation of negative pressure during ejection of the drug fluid during use. The air exchange vent may include a superhydrophobic filter, optionally in combination with a spiral vapor barrier, which provides for free exchange of air into and out of the reservoir.

[0087] In certain aspects of the disclosure, the ejector mechanism, reservoir, and housing/mouthpiece function to generate a plume with droplet diameters less than about 5 um. As discussed above, in certain embodiments, the reservoir and ejector mechanism modules are powered by electronics in the device housing and a reservoir which may carry sufficient drug for a single dose, just a few doses, or several hundred doses of medicament.

[0088] The present disclosure also provides an in-line droplet delivery device that is altitude insensitive. In certain implementations, the in-line droplet delivery device is configured so as to be insensitive to pressure differentials that may occur when the user travels from sea level to sub-sea levels and at high altitudes, e.g., while traveling in an airplane where pressure differentials may be as great as 4 psi. As will be discussed in further detail herein, in certain implementations of the disclosure, the in-line droplet delivery device may include a superhydrophobic filter, optionally in combination with a spiral vapor barrier, which provides for free exchange of air into and out of the reservoir, while blocking moisture

or fluids from passing into the reservoir, thereby reducing or preventing fluid leakage or deposition on aperture plate surfaces.

[0089] In certain aspects, the devices of the disclosure eliminate the need for patient / device coordination by using a differential pressure sensor to initiate the piezoelectric ejector in response to the onset of inhalation. The device does not require manual triggering of medication delivery. Unlike propellant driven MDIs, the droplets from the devices of the disclosure are generated having little to no intrinsic velocity from the aerosol formation process and are inspired into the lungs solely by the user's incoming breath passing through the mouthpiece. The droplets will ride on entrained air providing improved deposition in the lung.

[0090] In certain embodiments, as described in further detail herein, when the drug ampoule is mated to the handheld base unit, electrical contact is made between the base containing the batteries and the ejector mechanism embedded in the drug reservoir. In certain embodiments, visual indications, e.g., a horizontal series of three user visible LED lights, and audio indications via a small speaker within the handheld base unit may provide user notifications. By way of example, the device may be, e.g., 2.0 -3.5 cm high, 5-7 cm wide, 10.5-12 cm long and may weight approximately 95 grams with an empty drug ampoule and with batteries inserted.

[0091] As described herein, in certain embodiments, the in-line droplet delivery device may be turned on and activated for use by inserting the drug ampoule into the base unit, opening the mouthpiece cover, and/or switching an on/off switch/slide bar. In certain embodiments, visual and/or audio indicators may be used to indicate the status of the device in this regard, e.g., on, off, stand-by, preparing, etc. By way of example, one or more LED lights may turn green and/or flash green to indicate the device is ready for use. In other embodiments, visual and/or audio indicators may be used to indicate the status of the drug ampoule, including the number of doses taken, the number of doses remaining, instructions for use, etc. For example, and LED visual screen may indicate a dose counter numerical display with the number of remaining doses in the reservoir.

[0092] As described in further detail herein, during use as a user inhales through the mouthpiece of the housing of an in-line droplet delivery device of the disclosure, a differential pressure sensor within the housing detects inspiratory flow, e.g., by measuring the pressure drop across a Venturi plate at the back of the mouthpiece. When a threshold pressure decline (e.g., 8 slm) is attained, the microprocessor activates the ejector mechanism, which in turn generates an ejected stream of droplets into the airflow of the device that the

user inhales through the mouthpiece. In certain embodiments, audio and/or visual indicates may be used to indicate that dosing has been initiated, e.g., one or more LEDs may illuminate green. The microprocessor then deactivates the ejector at a designated time after initiation so as to achieve a desired administration dosage, e.g., 1-1.45 seconds. In certain embodiments, as described in further detail herein, the device may provide visual and/or audio indicators to facilitate proper dosing, e.g., the device may emit a positive chime sound after the initiation of dosing, indicating to the user to begin holding their breath for a designated period of time, e.g., 10 seconds. During the breath hold period, e.g., the three green LEDs may blink. Additionally, there may be voice commands instructing the patient on proper times to exhale, inhale and hold their breath, with an audio indicator of a breath hold countdown.

[0093] Following dosing, the in-line droplet delivery device may turned off and deactivated in any suitable manner, e.g., by closing the mouthpiece cover, switching an on/off switch/slide bar, timing out from non-use, removing the drug ampoule, etc. If desired, audio and/or visual indicators may prompt a user to deactivate the device, e.g., by flashing one or more red LED lights, providing voice commands to close the mouthpiece cover, etc.

[0094] In certain embodiments, the in-line droplet delivery device may include an ejector mechanism closure system that seals the aperture plate when not in use to protect the integrity of the aperture plate and to minimize and prevent contamination and evaporation of the fluid within the reservoir. For example, in some embodiments, the device may include a mouthpiece cover that comprises a rubber plug that is sized and shaped to seal the exit side surface of the aperture plate when the cover is closed. In other embodiments, the mouthpiece cover may trigger a slide to seal the exit side surface of the aperture plate when the cover is closed. Other embodiments and configurations are also envisioned, e.g., manual slides, covers, and plugs, etc. In certain aspects, the microprocessor may be configured to detect when the ejector mechanism closure, aperture plate seal, etc. is in place, and may thereafter deactivate the device.

[0095] Several features of the device allow precise dosing of specific droplet sizes. Droplet size is set by the diameter of the holes in the mesh which are formed with high accuracy. By way of example, the holes in the aperture plate may range in size from 1 μm to 6 μm, from 2 μm to 5 μm, from 3 μm to 5 μm, from 3 μm to 4 μm, etc. Ejection rate, in droplets per second, is generally fixed by the frequency of the aperture plate vibration, e.g., 108-kHz, which is actuated by the microprocessor. In certain embodiments, there is less than a 50-millisecond lag between the detection of the start of inhalation and full droplet generation.

[0096] Other aspects of the device of the disclosure that allow for precise dosing of specific droplet sizes include the production of droplets within the respirable range early in the inhalation cycle, thereby minimizing the amount of drug product being deposited in the mouth or upper airways at the end of an inhalation. In addition, the design of the drug ampoule allows the aperture plate surface to be wetted and ready for ejection without user intervention, thus obviating the need for shaking and priming. Further, the design of the drug ampoule vent configuration together with the ejector mechanism closure system limits fluid evaporation from the reservoir to less than 150 μL to 350 μL per month.

[0097] The device may be constructed with materials currently used in FDA cleared devices. Standard manufacturing methods may be employed to minimize extractables.

[0098] Any suitable material may be used to form the housing of the droplet delivery device. In particular embodiment, the material should be selected such that it does not interact with the components of the device or the fluid to be ejected (e.g., drug or medicament components). For example, polymeric materials suitable for use in pharmaceutical applications may be used including, e.g., gamma radiation compatible polymer materials such as polystyrene, polysulfone, polyurethane, phenolics, polycarbonate, polyimides, aromatic polyesters (PET, PETG), etc.

[0099] The drug ampoule may be constructed of any suitable materials for the intended pharmaceutical use. In particular, the drug contacting portions may be made from material compatible with the desired active agent(s), e.g., albuterol sulfate and ipratropium bromide. By way of example, in certain embodiments, the drug only contacts the inner side of the drug reservoir and the inner face of the aperture plate and piezoelectric element. Wires connecting the piezoelectric ejector mechanism to the batteries contained in the base unit may be embedded in the drug ampoule shell to avoid contact with the drug. The piezoelectric ejector may be attached to the drug reservoir by a flexible bushing. To the extent the bushing may contact the drug fluid, it may be, e.g., any suitable material known in the art for such purposes such as those used in piezoelectric nebulizers.

[00100] In certain embodiments, the device mouthpiece may be removable, replaceable and may be cleaned. Similarly, the device housing and drug ampoule can be cleaned by wiping with a moist cloth. In certain embodiments, the mouthpiece may be interfaced with (and optionally removable and/or replaceable), integrated into, or part of the housing. In other embodiments, the mouthpiece may be interfaced with (and optionally removable and/or replaceable), integrated into, or part of the drug delivery ampoule.

[00101] Again, any suitable material may be used to form the mouthpiece of the droplet delivery device. In particular embodiment, the material should be selected such that it does not negatively interact with the components of the device or the fluid to be ejected (e.g., drug or medicament components). For example, polymeric materials suitable for use in pharmaceutical applications may be used including, e.g., gamma radiation compatible polymer materials such as polystyrene, polysulfone, polyurethane, phenolics, polycarbonate, polyimides, aromatic polyesters (PET, PETG), etc. In certain embodiments, the mouthpiece may be removable, replaceable and sterilizable. This feature improves sanitation for drug delivery by providing a mechanism to minimize buildup of aerosolized medication within the mouthpiece and by providing for ease of replacement, disinfection and washing. In one embodiment, the mouthpiece tube may be formed from sterilizable and transparent polymer compositions such as polycarbonate, polyethylene or polypropylene, as discussed herein.

[00102] In certain aspects of the disclosure, an electrostatic coating may be applied to the one or more portions of the housing, e.g., inner surfaces of the housing along the airflow pathway such as the mouthpiece, to aid in reducing deposition of ejected droplets during use due to electrostatic charge build-up. Alternatively, one or more portions of the housing may be formed from a charge-dissipative polymer. For instance, conductive fillers are commercially available and may be compounded into the more common polymers used in medical applications, for example, PEEK, polycarbonate, polyolefins (polypropylene or polyethylene), or styrenes such as polystyrene or acrylic-butadiene-styrene (ABS) copolymers. Alternatively, in certain embodiments, one or more portions of the housing, e.g., inner surfaces of the housing along the airflow pathway such as the mouthpiece, may be coated with anti-microbial coatings, or may be coated with hydrophobic coatings to aid in reducing deposition of ejected droplets during use. Any suitable coatings known for such purposes may be used, e.g., polytetrafluoroethylene (Teflon).

[00103] Any suitable differential pressure sensor with adequate sensitivity to measure pressure changes obtained during standard inhalation cycles may be used, e.g., ± 5 SLM, 10 SLM, 20 SLM, etc. For instance, pressure sensors from Sensirion, Inc., SDP31 or SDP32 (US 7,490,511 B2) are particularly well suited for these applications.

[00104] In certain aspects, the microprocessor in the device may be programmed to ensure exact timing and actuation of the ejector mechanism in accordance with desired parameters, e.g., based duration of piezoelectric activation to achieve desired dosages, etc. In certain embodiments, the device includes or interfaces with a memory (on the device, smartphone, App, computer, etc.) to record the date-time of each ejection event, as well as the

user's inhalation flow rate during the dose inhalation to facilitate user monitoring, as well as drug ampoule usage monitoring. For instance, the microprocessor and memory can monitor doses administered and doses remaining in a particular drug ampoule. In certain embodiments, the drug ampoule may comprise components that include identifiable information, and the base unit may comprise components that may "read" the identifiable information to sense when a drug ampoule has been inserted into the base unit, e.g., based on a unique electrical resistance of each individual ampoule, an RFID chip, or other readable microchip (e.g., cryptoauthentication microchip). Dose counting and lockouts may also be preprogramed into the microprocessor.

[00105] In certain embodiments of the present disclosure, the signal generated by the pressure sensors provides a trigger for activation and actuation of the ejector mechanism to thereby generate droplets and delivery droplets at or during a peak period of a patient's inhalation (inspiratory) cycle and assures optimum deposition of the plume of droplets and delivery of the medication into the pulmonary airways of the user.

[00106] In accordance with certain aspects of the disclosure, the in-line droplet delivery device provides a reliable monitoring system that can date and time stamp actual deliver of medication, e.g., to benefit patients through self-monitoring or through involvement of care givers and family members.

[00107] As described in further detail herein, the in-line droplet delivery device of the disclosure may detect inspiratory airflow and record/store inspiratory airflow in a memory (on the device, smartphone, App, computer, etc.). A preset threshold (e.g., 8-10 slm) triggers delivery of medication over a defined period of time, e.g., 1-1.5 seconds. Inspiratory flow is sampled frequently until flow stops. The number of times that delivery is triggered is incorporated and displayed in the dose counter LED on the device. Blue tooth capabilities permit the wireless transmission of the data.

[00108] Bluetooth communication in the device will communicate date, time and number of actuations per session to the user's smartphone. Software programing can provide charts, graphics, medication reminders and warnings to patients and whoever is granted permission to the data. The software application will be able to incorporate multiple medications that use the device of the disclosure.

[00109] The device of the disclosure can also provide directed instruction to users, including audio and visual indicators to facilitate proper use of the device and proper dosing. For instance, certain patients that may need drug to be delivered to an inflamed and narrowed lower respiratory region are typically asked to inhale drug particles slowly and steadily

followed by about ten seconds of holding their breath to allow sedimentation to occur. In a medical office these patients can be coached and encouraged to hold their breath after inhalation. However, outside of a medical care setting, improper use of an inhaler device often results.

[00110] The device of the present disclosure is configured to dispense droplets during the correct part of the inhalation cycle, and can including instruction and/or coaching features to assist patients with proper device use, e.g., by instructing the holding of breath for the correct amount of time after inhalation. The device of the disclosure allows this dual functionality because it may both monitor air flow during the inhalation, and has internal sensors/controls which may detect the end of inhalation (based upon measured flow rate) and can cue the patient to hold their breath for a fixed duration after the inhalation ceases.

[00111] In one exemplary embodiment, a patient may be coached to hold their breath with an LED that is turned on at the end of inhalation and turned off after a defined period of time (i.e., desired time period of breath hold), e.g., 10 seconds. Alternatively, the LED may blink after inhalation, and continue blinking until the breath holding period has ended. In this case, the processing in the device detects the end of inhalation, turns on the LED (or causes blinking of the LED, etc.), waits the defined period of time, and then turns off the LED. Similarly, the device can emit audio indications, e.g., one or more bursts of sound (e.g., a 50 millisecond pulse of 1000 Hz), verbal instructions to hold breath, verbal countdown, music, tune, melody, etc., at the end of inhalation to cue a patient to hold their breath for the during of the sound signals. If desired, the device may also vibrate during or upon conclusion of the breath holding period.

[00112] In certain embodiments, the device provides a combination of audio and visual methods (or sound, light and vibration) described above to communicate to the user when the breath holding period has begun and when it has ended. Or during the breath holding to show progress (e.g., a visual or audio countdown).

[00113] In other aspects, the device of the disclosure may provide coaching to inhale longer, more deeply, etc. The average peak inspiratory flow during inhalation (or dosing) can be utilized to provide coaching. For example, a patient may hear a breath deeper command until they reach 90% of their average peak inspiratory flow as measured during inspiration (dosing) as stored on the device, phone or in the cloud.

[00114] In addition, an image capture device, including cameras, scanners, or other sensors without limitation, e.g. charge coupled device (CCD), may be provided to detect and measure the ejected aerosol plume. These detectors, LED, delta P transducer, CCD device,

all provide controlling signals to a microprocessor or controller in the device used for monitoring, sensing, measuring and controlling the ejection of a plume of droplets and reporting patient compliance, treatment times, dosage, and patient usage history, etc., via Bluetooth, for example.

[00115] Reference will now be made to the figures, with like components illustrates with like references numbers.

[00116] **FIGS. 1A** and **1B** illustrate an exemplary in-line droplet delivery device of the disclosure, with **FIG. 1A** showing the in-line droplet delivery device 100 having a mouthpiece cover 102 in the closed position, and **FIG. 1B** having a mouthpiece cover 102 in the open position. As shown, the droplet delivery device is configured in an in-line orientation in that the housing, its internal components, and various device components (e.g., the mouthpiece, air inlet flow element, etc.) are orientated in a substantially in-line or parallel configuration (e.g., along the airflow path) so as to form a small, hand-held device.

[00117] In the embodiment shown in **FIGS. 1A** and **1B**, the in-line droplet delivery device 100 includes a base unit 104 and a drug delivery ampoule 106. As illustrated in this embodiment, and discussed in further detail herein, the drug delivery ampoule 106 slides into the front of the base unit 104 via slides 112. In certain embodiments, mouthpiece cover 102 may include a push element 102a that facilitates insertion of drug delivery ampoule 106. Also illustrated are one or more airflow entrances or openings 110. By way of example, there may be airflow entrances on the opposite side of the device, multiple airflow entrances on the same side of the device, or a combination thereof (not shown). The in-line droplet delivery device 100 also includes mouthpiece 108 at the airflow exit side of the device.

[00118] With reference to **FIG. 2**, an exploded view of the exemplary in-line droplet delivery device of **FIGS. 1A** and **1B** is shown, including internal components of the housing including a power/activation button 201; an electronics circuit board 202; a drug delivery ampoule 106 that comprises an ejector mechanism and reservoir (not shown); and a power source 203 (e.g., three AAA batteries, which may optionally be rechargeable) along with associated contacts 203a. In certain embodiments, the reservoir may be single-unit dose or multi-unit dose that may be replaceable, disposable or reusable. Also shown, one or more pressure sensors 204 and optional spray sensors 205. In certain embodiments, the device may also include various electrical contacts 210 and 211 to facilitate activation of the device upon insertion of drug delivery ampoule 106 into the base unit. Likewise, in certain embodiments, the device may include slides 212, posts 213, springs 214, and ampoule lock 215 to facilitate insertion of drug delivery ampoule 106 into the base unit.

[00119] The components may be packaged in a housing, and generally oriented in an in-line configuration. The housing may be disposable or reusable, single-dose or multi-dose. Although various configurations to form the housing are within the scope of the disclosure, as illustrated in **FIG. 2**, the housing may comprise a top cover 206, a bottom cover 207, and an inner housing 208. The housing may also include a power source housing or cover 209.

[00120] In certain embodiments, the device may include audio and/or visual indications, e.g., to provide instructions and communications to a user. In such embodiments, the device may include a speaker or audio chip (not shown), one or more LED lights 216, and LCD display 217 (interfaced with an LCD control board 218 and lens cover 219). The housing may be handheld and may be adapted for communication with other devices via a Bluetooth communication module or similar wireless communication module, e.g., for communication with a subject's smart phone, tablet or smart device (not shown).

[00121] In certain embodiments, an air inlet flow element (not shown, see, e.g., **FIGS. 5A-5C** and **FIGS. 11A-18D**) may be positioned in the airflow at the airflow entrance of the housing and configured to facilitate non-turbulent (i.e., laminar and/or transitional) airflow across the exit side of aperture plate and to provide sufficient airflow to ensure that the ejected stream of droplets flows through the droplet delivery device during use. In some embodiments, the air inlet flow element may be positioned within the mouthpiece. Aspects of the present embodiment further allows customizing the internal pressure resistance of the particle delivery device by allowing the placement of laminar flow elements having openings of different sizes and varying configurations to selectively increase or decrease internal pressure resistance, as will be explained in further detail herein.

[00122] By way of non-limiting example, an exemplary method of insertion of an ampoule through to use and powering off of the device may be performed as follows:

1. When a new ampoule is initially inserted and pushed onto the device slide guide the device door is open and the ampoule slides and clicks into ampoule position 1. At this setting, an aperture plate seal or cover on the ampoule is open and electrical contacts on the device and ampoule make contact. The system is powered ON and ready for breath actuation. When the device door is opened, an audible beep may be emitted and LED indicator(s) may turn green or flash to notify the user that the system is ON and ready for dosing by inhaling through the mouthpiece.

2. As a patient inhales, a pre-set pressure value is reached and detected by the pressure sensor located within the housing (e.g., delta P sensor) and a second audible indicator or LED indicator may now indicate that a dose is triggered. After the dose is

triggered and delivered, another audible and/or LED indicator may trigger until a spray cycle time of, e.g., 1-5 seconds (or other designated dosing time) ends. Further, if desired, when a dose is delivered, the dose counter displayed on the LCD will indicate that a dose was delivered by a decrease in number of doses displayed on the LCD.

3. If no additional doses are required and a time of, e.g., 15 seconds elapse, an audible and/or LED indicator may trigger to alert the user that the device is about to power-off, after which time the device may enter into a low power, sleep mode.

4. If no additional doses are required, the device door is closed to push the ampoule to the non-use position, the aperture plate seal or cover is closed and the device is in placed sleep mode. Further, as the slide mechanism releases pressure from the ON/OFF switch, and the system is now OFF.

5. When a patient is ready to apply additional doses, the device door is opened and the ampoule slides towards the mouthpiece as it is pushed by a spring-loaded mechanism from the non-use position to the use position, to thereby open the aperture plate seal or cover.

[00123] More particularly, a specific exemplary embodiment of a mode of operation of insertion of a drug ampoule and operation of a device is illustrated in **FIGS. 3A-1** to **FIG. 3C-3**. Referring to **FIG. 3A-**1 and **3A-2**, when a drug ampoule (1), is initially inserted and pushed onto the device slide guide (1a), the device door (2) is open, the ampoule slides and clicks into ampoule position 1. An oval button (ampoule lock) (1b) clicks down and snaps back to lock the ampoule in place. At this setting, the seal on the aperture plate is open, the four electrical contacts on the device and ampoule make contact, and the system is powered ON, ready for breath actuation. The front two contacts (3) complete the circuit to actuate the piezoelectric element, while the rear two contacts (4) are used to provide specific information on the ampoule, such as ampoule ID, drug type, dosage, etc.

[00124] Referring to **FIG. 3B-1** and **3B-2**, ampoule position 1(A) is shown, in which the oval button (1b) locks the ampoule into place and the four electrical contacts, front (3) and rear (4) connect to complete the electric circuit. When the ampoule is in position 1, the electronic component that activates the ON/OFF button (1c) is pushed by the spring-loaded, slide mechanism (5). **FIG. 3B-1** provides a bottom view of the spring-loaded slide mechanism (5) and the ON/OFF button (1c), in the ON mode. **FIG. 3B-2** provides an exploded view (5a) of side brackets on the spring-loaded slide (5) and their position (5a- dash arrows) through slots (5b) on the device which make contact on the ampule (5c) to push the

ampule forward when the device door is opened and activate the ON/OFF switch (1c) as it makes contact with the ON/OFF button (1d). The device ON/OFF button (1c) is activated by the slide (5) when the mouthpiece cover (2) is closed and pushes the ampule back to position 2, where the aperture plate seal is in the closed position and power is turned OFF to the device as pressure on the ON/OFF switch is released.

[00125] Referring to **FIG. 3C-1, 3C-2**, and **3C-3**, cross-sections of the device with the ampoule inserted are illustrated to better illustrate the ampoule slide mechanism and positioning of the ON/OFF switch. **FIG. 3C-1** shows ampoule position 1, with the mouthpiece cover in the open position and the ON/OFF switch in the ON position. **FIG. 3C-2** shows ampoule position 2, with the mouthpiece cover in the closed position and the ON/OFF switch in the OFF position. **FIG. 3C-3** shows ampoule position 2, with the mouthpiece cover in the open position and the ON/OFF switch in the OFF position.

[00126] However, it is noted that the devices and methods of the disclosure are not so limited, and various modifications and expansions of the method of operation is envisioned as within the scope of the disclosure.

[00127] In another embodiment, **FIGS. 4A** and **4B** illustrate an alternative in-line droplet delivery device of the disclosure, with **FIG. 4A** showing the in-line droplet delivery device 400 with a base unit 404 having a mouthpiece cover 402 in the closed position, and **FIG. 4B** with a base unit 404 having a mouthpiece cover 402 in the open position. As shown, the droplet delivery device is configured in an in-line orientation in that the housing, its internal components, and various device components (e.g., the mouthpiece, air inlet flow element, etc.) are orientated in a substantially in-line or parallel configuration (e.g., along the airflow path) so as to form a small, hand-held device.

[00128] In the embodiment shown in **FIGS. 4A** and **4B**, the in-line droplet delivery device 400 includes a base unit 404 and a drug delivery ampoule 406. As illustrated in this embodiment, and discussed in further detail herein, the drug delivery ampoule 406 slides into the front of the base unit 404. In certain embodiments, mouthpiece cover 402 may include aperture plate plug 412. Also illustrated are one or more airflow entrances or openings 410 in mouthpiece 408. By way of example, there may be airflow entrances on the opposite side of the device, multiple airflow entrances on the same side of the device, or a combination thereof (not shown). The in-line droplet delivery device 400 also includes mouthpiece 408 at the airflow exit side of the device.

[00129] With reference to **FIG. 5**, an exploded view of the exemplary in-line droplet delivery device of **FIGS. 4A** and **4B** is shown, including internal components of the housing

including an electronics circuit board 502; a drug delivery ampoule 406 that comprises top cover 430 having optional vents 431 and vapor barriers 432, an ejector mechanism 434, a drug reservoir 435, electrical contacts 436, and one or more sensor ports 437; and a power source 503 (e.g., three AAA batteries, which may optionally be rechargeable). In certain embodiments, the device may also include various electrical contacts 442 and sensor ports 444 to facilitate activation of the device upon insertion of drug delivery ampoule 406 into the base unit 404. Likewise, in certain embodiments, the device may include resistors or chips 504 to facilitate insertion and detection of drug delivery ampoule 406 into the base unit 404.

[00130] In certain embodiments, the reservoir may be single-unit dose or multi-unit dose that may be replaceable, disposable or reusable. As illustrated in **FIG. 5**, in certain embodiments, the drug delivery ampoule may also comprise or be interfaced with a mouthpiece 408 and a mouthpiece cover 402. As shown, ejector mechanism 434 may be positioned in line with mouthpiece 408 and drug reservoir 435 such that the exit side of the aperture plate is perpendicular to the direction of airflow and the stream of droplets is ejected in parallel to the direction of airflow. The mouthpiece cover 402 may further include an aperture plate plug 412.

[00131] The components may be packaged in a housing, and generally oriented in an in-line configuration. The housing may be disposable or reusable, single-dose or multi-dose. Although various configurations to form the housing are within the scope of the disclosure, as illustrated in **FIG. 5**, the housing may comprise a top cover 506, a bottom cover 507, and an inner housing 508. The device may also include one or more ampoule release buttons 550, e.g., positioned on the side of the housing to facilitate release of the drug delivery ampoule 406 once inserted into the base unit 404.

[00132] In certain embodiments, the device may include audio and/or visual indications, e.g., to provide instructions and communications to a user. In such embodiments, the device may include a speaker or audio chip 520, one or more LED lights 516, and LCD display 517 (interfaced with an LCD control board 518 and lens cover 519). The housing may be handheld and may be adapted for communication with other devices via a Bluetooth communication module or similar wireless communication module, e.g., for communication with a subject's smart phone, tablet or smart device (not shown).

[00133] With reference to **FIG. 6**, a cross-section of an in-line device of **FIGS. 4A** and **4B** is shown to illustrate an exemplary configuration of the interior of the drug reservoir 435 and its relation to ejector mechanism 434. As shown, drug reservoir 435 may be sized and shaped such that the volume of fluid held within the reservoir is funneled and directed to the

ejection surface of the aperture plate during use. More particularly, as shown, the bottom surface of the drug reservoir may be sloped towards the ejector mechanism so as to facilitate flow of the fluid within the drug reservoir during use. Without intending to be limited by theory, such configurations may be particularly suited for device orientations wherein the ejector mechanism is oriented perpendicularly to the direction of airflow. However, it is noted that the disclosure is not so limited, and various shapes, sizes and configurations of ampoule are envisioned as within the scope of the disclosure.

[00134] **FIG. 7** illustrates the base unit 404 of the embodiment of **FIGS. 4A** and **4B** without the drug delivery ampoule inserted. Without the drug delivery ampoule inserted, tracks 440 for directing the ampoule into place, electrical contacts 442, and sensor port 444 are shown. Also shown is release button 450.

[00135] **FIGS. 8A** and **8B** illustrate a drug delivery ampoule 406 with mouthpiece cover 402 attached and in a closed position in front view (**FIG. 8A**) and back view (**FIG. 8B**). **FIG. 8B** illustrates electrical contacts 436 and sensor port 437 of the ampoule, as well as protruding slides 452 to facilitate placement of the ampoule into tracks 440 during insertion. By way of example, when drug delivery ampoule 406 is inserted into base unit 404, protruding slides 452 mate with tracks 440, sensor port 437 mates with sensor port 444, and electrical contacts 436 mates with electrical contacts 442. The drug delivery ampoule is pushed into the base unit and locked into place with the protruding slides and tracks engaging one another. During use, a pressure sensor located on the control board senses pressure changes within the device via the pressure sensing ports (e.g., within the mouthpiece). To facilitate detection of pressure changes, the base unit includes a second pressure sensing port and outside channel (not shown) to facilitate sensing of reference or ambient pressure.

[00136] As discussed herein, the drug reservoir and/or drug delivery ampoule may include various vents and/or vapor barriers to facilitate venting, etc. With reference to **FIGS. 9A-9C**, an exemplary reservoir or ampoule is shown which is configured so as to be insensitive to pressure differentials that may occur when the user travels from sea level to sub-sea levels and at high altitudes, e.g., while traveling in an airplane where pressure differentials may be as great as 4 psi. As shown, **FIG. 9A** shows a perspective view of an exemplary ampoule 900. FIGS 9B and 9C show exploded view of ampoule 900 from perspective top and bottom views. With reference to **FIGS. 9B** and **9C**, the ampoule 900 generally includes a top cover 901 and a bottom cover 902. The ampoule 900 may be configured to include one or more superhydrophobic filter(s) 904 covering one or more vents 906, and the fluid reservoir housing may include a spiral channel (or similarly shaped) vapor

barrier 905, which provides for free exchange of air into and out of the fluid reservoir, while blocking moisture or fluids from passing into the reservoir, thereby reducing or preventing fluid leakage or deposition on aperture plate surfaces. If desired, one or more O-rings 903, or similar sealing mechanism, may be used to form a seal between the top cover 901 and the bottom cover 902 in connection with the vapor barrier 905. Without intending to be limited, the superhydrophobic filter and vent may generally allow for the venting of air and equilibration of air pressure within the fluid reservoir, while maintaining a sterile environment within the fluid reservoir. The spiral channel vapor barrier will generally prevent the transfer of moisture to and from the fluid reservoir (e.g., through the vent opening).

[00137] In another embodiment, shown in **FIG. 9D**, a cross-section of an exemplary small volume drug ampoule 910 is illustrated. As shown, the small volume drug ampoule 910 includes a membrane 920, which separates the reservoir into two volumes, a first background pressure fluid volume 925, and a second drug fluid volume 930. The small volume ampoule may also include an air exchange vent (e.g., a superhydrophobic filter) 935, and an option fill port 940. Any suitable size and shape configuration of reservoir may be used. By way of non-limiting example, for 20 uL dose on a 5 mm ejector, a small volume ampoule may be sized and shaped so as to be 5 mm diameter by 1 mm high well.

[00138] In accordance with aspects, the in-line droplet delivery devices of the disclosure may include an air inlet flow element (see, e.g., **FIGS. 10A-10C** and **12A-19D**) which may be positioned in the airflow at the airflow entrance of the device and configured to facilitate non-turbulent (i.e., laminar and/or transitional) airflow across the exit side of aperture plate and to provide sufficient airflow to ensure that the ejected stream of droplets flows through the droplet delivery device during use. In some embodiments, the air inlet flow element may be positioned within the mouthpiece. Aspects of the present embodiment further allows customizing the internal pressure resistance of the particle delivery device by allowing the placement of laminar flow elements having openings of different sizes and varying configurations to selectively increase or decrease internal pressure resistance, as will be explained in further detail herein.

[00139] In accordance with certain embodiments of the in-line droplet delivery device of the disclosure, the device may include an air inlet flow element may be positioned in the airflow at the airflow entrance of the device and configured to facilitate non-turbulent (i.e., laminar and/or transitional) airflow across the exit side of aperture plate and to provide sufficient airflow to ensure that the ejected stream of droplets flows through the droplet

delivery device during use. In some embodiments, the air inlet flow element may be positioned within the mouthpiece. In addition, the air inlet flow element allows for customization of internal device pressure resistance by designing openings of different sizes and varying configurations to selectively increase or decrease internal pressure resistance.

[00140] As will be described in further detail herein, the air inlet flow element may be positioned behind the exit side of the aperture plate along the direction of airflow, or in-line or in front of the exit side of the aperture plate along the direction of airflow. In certain embodiments, the air inlet flow element comprises one or more openings formed there through and configured to increase or decrease internal pressure resistance within the droplet delivery device during use. For instance, the air inlet flow element comprises an array of one or openings. In the embodiments, the air inlet flow element comprises one or more baffles, e.g., wherein the one or more baffles comprise one or more airflow openings.

[00141] In certain embodiments, the air inlet flow element is designed and configured in order to provide an optimum airway resistance for achieving peak inspirational flows that are required for deep inhalation which promotes delivery of ejected droplets deep into the pulmonary airways. Air inlet flow elements also function to promote non-turbulent flow across the aerosol plume exit port, which also serves to stabilize airflow repeatability, stability and insures an optimal precision in the delivered dose.

[00142] Without intending to be limited by theory, in accordance with aspects of the disclosure, the size, number, shape and orientation of flow restrictions (e.g., openings, holes, flow blocks, etc.) in the air inlet flow element of the disclosure may be configured to provide a desired pressure drop within the in-line droplet delivery device. In certain embodiments, it may be generally desirable to provide a pressure drop that is not so large as to strongly affect a user's breathing or perception of breathing.

[00143] In certain implementations, the use of air inlet flow elements having differently configured, sized, and shaped flow restrictions (e.g., openings, holes, flow blocks, etc.), or the use of adjustable apertures may be required in order to accommodate the differences among the lungs and associated inspiratory flow rates of young and old, small and large, and various pulmonary disease states. For example, if the aperture is adjustable by the patient (perhaps by having a slotted ring that can be rotated), then a method may be provided to read the aperture hole setting and lock that position to avoid inadvertent changes of the aperture hole size, hence the flow measurement. Although pressure sensing is an accurate method for flow measurement, other embodiments may use, e.g., hot wires or thermistor types of flow rate measurement methods which lose heat at a rate proportional to flow rate,

moving blades (turbine flow meter technology) or by using a spring-loaded plate, without limitation of example.

[00144] For instance, **FIGS. 10A-10C** illustrate certain exemplary air inlet flow elements of the disclosure. **FIGS. 10A-10C** also illustrate the position of pressure sensors, the mouthpiece, and air channels for reference pressure sensing. However, the disclosure is not so limited, and other configurations including those described herein are contemplated as within the scope of the disclosure. While not being so limited, the air inlet flow elements of **FIGS. 10A-10C** are particularly suitable for use with the in-line droplet delivery devices of **FIGS. 1A-1B**.

[00145] More particularly, **FIG. 10A** illustrates a cross-section of a partial in-line droplet delivery device 1000 of the disclosure including a mouthpiece cover 1001, a mouthpiece 1002, a drug delivery ampoule 1003 comprising a drug reservoir 1004 and an ejector mechanism 1005. As illustrated, the droplet delivery device includes an air inlet flow element 1006 having an array of holes 1006a at the air entrance of the mouthpiece 1002. Also shown is a pressure sensor port 1007, which may be used to sense a change in pressure within the mouthpiece. With reference to **FIG. 10B**, a front view of the device 1000 is illustrated, wherein a second pressure sensor port 1008 is shown to provide for sensing of a reference or ambient pressure.

[00146] **FIG. 10C** illustrates a partial exploded view including mouthpiece 1002 and inner housing 1011. As shown, mouthpiece 1002 includes air intake flow element 1006 with an array of holes 1006a, and pressure sensor port 1007. Further, mouthpiece 1002 may include an ejection port 1114 positioned, e.g., on the top surface of the mouthpiece so as to align with the ejector mechanism to allow for ejection of the stream of droplets into the airflow of the device during use. Other sensor ports 1115 may be positioned as desired along the mouthpiece to allow for desired sensor function, e.g., spray detection. The mouthpiece may also include positioning baffle 1116 that interfaces with the base unit upon insertion. Inner housing 1011 includes pressure sensor board 1009 and outside channel 1010 for facilitating sensing of reference or ambient pressure. The inner housing further includes a first pressure sensing port 1112 to facilitate sensing of pressure changes within the device (e.g., within the mouthpiece or housing), and a second pressure sensing port 1113 to facilitate sensing of reference or ambient pressure.

[00147] In this regard, **FIG. 11A** illustrates differential pressure as a function of flow rates through exemplary air inlet flow elements similar to that of **FIGS. 10A-10C** as a function of number of holes (29 holes, 23 holes, 17 holes). Referring to **FIG. 11B**, the flow

rate verses differential pressure as a function of hole size is shown to have a liner relationship, when flow rate is plotted as a function of the square root of differential pressure. The number of holes is held constant at 17 holes. These data provide a manner to select a design for an air inlet flow element to provide a desired pressure resistance, as well as provide a model for the relationship between flow rate and differential pressure, as measured in an exemplary droplet delivery device.

Inspiratory Flow Rate (SLM) = C(SqRt) (Pressure(Pa))

Element #	Hole Size (mm) (17 holes)	Pressure at 10 slm (Pa)	Flow at 1000 Pa	Equation Constant (C)
0	1.9	6	149.56	4.73
1	2.4	2.1	169.48	5.36
2	2.7	1.7	203.16	6.43
3	3	1.3	274.46	8.68

[00148] A particular non-limiting exemplary air inlet flow element may 29 holes, each 1.9 mm in diameter. However, the disclosure is not so limited. For example, the air inlet flow element may have hole diameters ranging from, e.g., 0.1 mm in diameter to diameters equal to the cross sectional diameter of the air inlet tube (e.g., 0.5 mm, 1 mm, 1.5 mm, 2 mm, 2.5 mm, 3 mm, 3.5 mm, 4 mm, 4.5 mm, 5 mm, 5.5 mm, 6 mm, 6.5 mm, etc.), and number of holes may range from 1 to the number of holes, for example, to achieve the desire air flow resistance, e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 29, 30, 60, 90, 100, 150, etc.

[00149] **FIGS. 12A-19D** illustrate alternative embodiments of air inlet flow elements of the disclosure. **FIGS. 12A-19D** also illustrate exemplary positioning of air inlet flow elements within the airflow of a device, within the mouthpiece, as well as the interfacing of a mouthpiece including an air inlet flow element to an drug delivery ampoule.

[00150] **FIG. 12A** shows an exemplary drug delivery ampoule with a mouthpiece interfaced at the airflow exit side of the device. The mouthpiece includes two airflow entrances on the sides, but no internal air inlet flow elements to provide resistance to airflow. **FIG. 12B** shows a front cross-section and **12C** shows a side cross-section, with **FIG. 12D** showing the same views with exemplary dimensions. **FIGS. 13A** and **14A** show similarly configured mouthpieces with two airflow entrances on the sides, but no internal air inlet flow elements to provide resistance to airflow. Again, **FIGS. 13B** and **14B** show a front cross-section and 13C and 14C show a side cross-section, with **FIGS. 13D** and **14D** showing the same views with exemplary dimensions to illustrate the differences in configurations between the embodiments. For instance, the embodiment of **FIG. 12** has openings that are 6.6 mm

long and 2 mm high, the embodiment of **FIG. 13** has openings that are 7.9 mm long and 2.5 mm high, and the embodiment of **FIG. 14** has openings that are 8.1 mm long and 3 mm high. Of course, the disclosure is not limited to these specific dimensions, and varied dimensions and numbers of air inflow openings are envisions as within the scope of the disclosure.

[00151] **FIG. 15A** shows an exemplary drug delivery ampoule with a mouthpiece interfaced at the airflow exit side of the device. The mouthpiece includes two airflow entrances on the exterior sides of the mouthpiece, and two interior baffles with additional airflow entrances to provide resistance and modeling of airflow. **FIG. 15B** shows a front cross-section and **15C** shows a side cross-section, with **FIG. 15D** showing the same views with exemplary dimensions. **FIG. 16A** shows a similarly configured mouthpiece that includes two airflow entrances on the exterior sides of the mouthpiece, and two interior baffles with additional airflow entrances to provide resistance and modeling of airflow. However, the interior baffles of **FIG. 16A** are larger (10 mm in height) than that of **FIG. 15A** (5 mm in height). **FIG. 16B** shows a front cross-section and **16C** shows a side cross-section, with **FIG. 16D** showing the same views with exemplary dimensions.

[00152] **FIG. 17A** shows an exemplary drug delivery ampoule with a mouthpiece interfaced at the airflow exit side of the device. The mouthpiece includes two airflow entrances on the exterior sides of the mouthpiece, and a substantially concentric baffle (two arcs that form a circle with the top and bottom of the mouthpiece) with two additional airflow entrances to provide resistance and modeling of airflow. **FIG. 17B** shows a front cross-section and **17C** shows a side cross-section, with **FIG. 17D** showing the same views with exemplary dimensions. **FIG. 18A** shows a similarly configured mouthpiece with a substantially concentric interior baffle, but the interior baffle includes four airflow entrances to provide resistance and modeling of airflow. **FIG. 18B** shows a front cross-section and 18C shows a side cross-section, with **FIG. 18D** showing the same views with exemplary dimensions.

[00153] **FIG. 19A** shows an exemplary drug delivery ampoule with a mouthpiece interfaced at the airflow exit side of the device. The mouthpiece includes two airflow entrances on the exterior sides of the mouthpiece, and a substantially concentric baffle with two additional airflow entrances to provide resistance and modeling of airflow. In addition, the interior area of the mouthpiece between the concentric baffle and the wall of the mouthpiece includes an array element positioned above the airflow entrances to provide additional resistance and modeling to airflow. The array element is positioned in a parallel arrangement with the direction of airflow. Again, **FIG. 19B** shows a front cross-section and

19C shows a side cross-section, with **FIG. 19D** showing the same views with exemplary dimensions.

[00154] In accordance with the disclosure, it has been found that the presence of inner air inlet flow elements generally improve spray efficiency for exemplary fluid solutions (deionized water and albuterol solution. For instance, as shown in **FIG. 20**, at 30 SLM , inner air inlet flow elements increase spray efficiency from 47% to 66%, and orienting interior airflow entrances away from ejection streams improves spray efficiency to 80% or more. The mouthpiece and drug reservoir are a single unit and can be weighted before ejection (W1), after ejection (W2) and after drying (W3) the mouthpiece to measure the percentage of ejected drug that leaves the mouthpiece for delivery to a user. Spray efficiency = (W1-W2)/(W1-W3)

[00155] In certain aspects of the disclosure, the in-line device may be configured to protect the surface of the aperture plate, to minimize evaporation losses, and to minimize contamination while the device is closed and not in use. For instance, as described herein, when the reservoir/ampoule is in the closed position, the surface of the aperture plate of the ejector mechanism may be closed/sealed against the housing or the mouthpiece cover. However, in certain embodiments, when the reservoir/ampoule includes an O-ring or gasket to facilitate the seal of the surface of the aperture plate of the ejector mechanism, the sliding of the reservoir/ampoule between the open and closed position may, in certain aspects, create friction which needs to be overcome by a compression spring during opening and closing.

[00156] In one embodiment, friction between the ampoule O-ring and the device housing may be reduced by applying a compressive force between the ampoule and the device housing in the last few millimeters as the ampoule is closed. Thus, higher friction is limited to the first few millimeters during opening, when the compression spring is providing the highest force; and during the last few millimeters of closing when the ampoule door is almost closed and force on the door is easiest for the user to apply. Force applied as the door is almost closed also creates minimal reaction forces at the door's hinge, improving robustness of the device. Applying pressure to the O-ring over a shorter distance also reduces wear on the O-ring (or gasket).

[00157] Without being limited, in certain embodiments, applying a compressive sealing force during the last few millimeters of ampoule motion to the closed position can be accomplished by utilizing a ramp on either the ampoule or device side of the ampoule track which engages a budge on the opposite face (device for ampoule or ampoule for device) as the ampoule approaches the closed position. This can also be a pair of ramps which engage as

the ampoule approaches the closed position. In certain aspects, the point(s) of contact between the ampoule and device should be in alignment with the center of pressure of the O-ring to create a uniform sealing pressure. Note that to achieve enough compression for good sealing, the total vertical motion created by the ramp only needs to be in the range of 0.1 mm.

[00158] Alternatively to a sealing force generated by a fixed movement of the ampoule towards the device, a flexible compressive element can apply a downward force the rises as the ampoule approaches the closed position. By way of non-limiting example, this could be the ramp intersecting a flexible, rubber-like, material or a metallic or plastic spring, including a cantilever (leaf) spring that the ramp encounters as it arrives at the closed position of the ampule.

[00159] The compressive force applied to the O-ring does not have to be large, but sufficient for the compliant O-ring to seal against the surface roughness of the device surface. In certain embodiments, a more compliant material will require less compressive force to seal. Similarly, the O-ring can be made from a slippery material such as teflon-coated or teflon-encapsulated material to reduce the sliding friction of the ampule. Similarly, sealing may be done by a lip seal at the face.

[00160] **FIGS. 21A-21C** illustrate exemplary embodiments showing a ramp structure on the ampoule lip that presses the ampoule down and compresses the O-ring while in the "closed" position. Note, as illustrated the size of the ramp is greatly exaggerated. In one embodiment, the ramp may be about 0.1 to 0.2 mm high. **FIG**. 21A shows an end view showing ampule with lips that are engaged in track that is part of body of device. **FIG. 21B** shows how an ampoule moves from closed to open position. Mouthpiece and user to the right. **FIG. 21C** illustrates a side view of an ampoule in track with a ramp on a lip to force a aperture plate seal, showing a closed and open position.

[00161] In other embodiments, the surface of the aperture plate may be protected by the mouthpiece cover. For instance, as shown in **FIG. 21D**, mouthpiece cover 2100 may include aperture plate plug 2102 that is specifically sized and shaped so as to form a mating seal against the surface of the aperture plate 2104 when the cover is closed. In certain embodiments, the aperture plate plug 2102 may have a stepped shape such that the plug forms a seal against the surface of the housing around the aperture plate without putting direct pressure on the surface of the aperture plate.

[00162] In certain embodiments, as illustrated herein, the reservoir/cartridge module may include components that may carry information read by the housing electronics including key parameters such as ejector mechanism functionality, drug identification, and

information pertaining to patient dosing intervals. Some information may be added to the module at the factory, and some may be added at the pharmacy. In certain embodiments, information placed by the factory may be protected from modification by the pharmacy. The module information may be carried as a printed barcode or physical barcode encoded into the module geometry (such as light transmitting holes on a flange which are read by sensors on the housing). Information may also be carried by a programmable or non-programmable microchip on the module which communicates to the electronics in the housing.

[00163] By way of example, module programming at the factory or pharmacy may include a drug code which may be read by the device, communicated via Bluetooth to an associated user smartphone and then verified as correct for the user. In the event a user inserts an incorrect, generic, damaged, etc., module into the device, the smartphone might be prompted to lock out operation of the device, thus providing a measure of user safety and security not possible with passive inhaler devices. In other embodiments, the device electronics can restrict use to a limited time period (perhaps a day, or weeks or months) to avoid issues related to drug aging or build-up of contamination or particulates within the device housing.

[00164] The in-line droplet delivery device may further include various sensors and detectors to facilitate device activation, spray verification, patient compliance, diagnostic mechanisms, or as part of a larger network for data storage, big data analytics and for interacting and interconnected devices used for subject care and treatment, as described further herein. Further, the housing may include an LED assembly on a surface thereof to indicate various status notifications, e.g., ON/READY, ERROR, etc.

[00165] The airflow exit of the housing of the droplet delivery device through which the ejected plume of droplets exit as they are inhaled into a subject's airways, may be configured and have, without limitation, a cross sectional shape of a circle, oval, rectangular, hexagonal or other shape, while the shape of the length of the tube, again without limitation, may be straight, curved or have a Venturi-type shape.

[00166] In another embodiment (not shown), a mini fan or centrifugal blower may be located at the air inlet side of the laminar flow element or internally of the housing within the airsteam. The mini fan generally may provide additional airflow and pressure to the output of the plume. For patients with low pulmonary output, this additional airplume may ensure that the plume of droplets is pushed through the device into the patient's airway. In certain implementations, this additional source of airflow ensures that the plume exit port is swept clean of the droplets and also provides mechanism for spreading the particle plume into an

airflow which creates greater separation between droplets. The airflow provided by the mini fan may also act as a carrier gas, ensuring adequate dose dilution and delivery.

[00167] In other embodiments, the internal pressure resistance of the in-line droplet delivery device may be customized to an individual user or user group by modifying the mouthpiece tube design to include various configurations of air aperture grids or openings, thereby increasing or decreasing resistance to airflow through the device as the user inhales. For instance, different air entrance aperture sizes and numbers may be used to achieve different resistance values, and thereby different internal device pressure values. This feature provides a mechanism to easily and quickly adapt and customize the airway resistance of the particle delivery device to the individual patient's state of health or condition.

[00168] In another aspect of the disclosure, in certain embodiments, the in-line droplet delivery devices provide for various automation, monitoring and diagnostic functions. By way of example, as described above, device actuation may be provided by way of automatic subject breath actuation. Further, in certain embodiments, the device may provide automatic spray verification, to ensure that the device has generated the proper particle generation and provided to proper dosing to the subject. In this regard, the particle delivery device may be provided with one or more sensors to facilitate such functionality.

[00169] For instance, an airflow sensor located in the mouthpiece may measure inspiratory and expiratory flow rates. This sensor is placed so that it does not interfere with drug delivery or become a site for collection of residue or promote bacterial growth or contamination. A differential (or gage) pressure sensor downplume of a flow restrictor (e.g., air inlet flow element) measures airflow based upon the pressure differential between the inside of the mouthpiece relative to the outside air pressure. During inhalation (inspiratory flow) the mouthpiece pressure will be lower than the ambient pressure and during exhalation (expiratory flow) the mouthpiece pressure will be greater than the ambient pressure. The magnitude of the pressure differential during an inspiratory cycle is a measure of the magnitude of airflow and airway resistance at the air inlet end of the delivery tube.

[00170] Again, a Bluetooth communication module or similar wireless communication module may be provided in order to link the droplet delivery device to a smartphone or other similar smart devices (not shown). Bluetooth connectivity facilitates implementation of various software or App's which may provide and facilitate patient training on the use of the device. A major obstacle to effective inhaler drug therapy has been either poor patient adherence to prescribed aerosol therapy or errors in the use of an inhaler device. By providing a real time display on the smartphone screen of a plot of the patient's inspiratory cycle, (flow

rate versus time) and total volume, the patient may be challenged to reach a goal of total inspiratory volume that was previously established and recorded on the smartphone during a training session in a doctor's office. Bluetooth connectivity further facilitates patient adherence to prescribed drug therapy and promotes compliance by providing a means of storing and archiving compliance information, or diagnostic data (either on the smartphone or cloud or other large network of data storage) that may be used for patient care and treatment.

[00171] More specifically, in certain embodiments, the droplet delivery device may provide automatic spray verification via LED and photodetector mechanisms. For instance, an infra-red transmitter (e.g., IR LED, or UV LED < 280 nm LED), and infra-red or UV (UV with <280nm cutoff) photodetector may be mounted along the droplet ejection side of the device to transmit an infra-red or UV beam or pulse, which detects the plume of droplets and thereby may be used for spray detection and verification. The IR or UV signal interacts with the aerosol plume and can be used to verify that a plume of droplets has been ejected as well as provide a measure of the corresponding ejected dose of medicament. Examples include but not limited to, infrared 850 nm emitters with narrow viewing angles of either, 8, 10 and 12-degrees, (MTE2087 series) or 275 nm UV LED with a GaN photodetector for aerosol plume verification in the solar blind region of the spectra. Alternatively in some applications, the sub 280 nm LEDs (e.g. 260 nm LEDs) can be used to disinfect the spacer tube 128.

[00172] By way of example, the concentration of a medicament in the ejected fluid may be made, according to Beer's Law Equation (Absorbance = e L c), where, e is the molar absorptivity coefficient (or molar extinction coefficient) which is a constant that is associated with a specific compound or formulation, L is the path length or distance between LED emitter and photodetector, and c is the concentration of the solution. This implementation provides a measure of drug concentration and can be used for verification and a means and way to monitoring patient compliance as well as to detect the successful delivery of medication.

[00173] In another embodiment, spray verification and dose verification can be monitored by measuring the transmission of 850 nM to 950 nM light across the spray in a region where the droplets are not variably diluted with different inhalation flow rates. The average and alternating signals from the detector may be measured to calibrate and confirm the optical path (average signal) and detect the spray (alternating signal). In practice, the alternating signal can be measured by a 100 Hz low-pass filter between the detector and analog converter, sampling the signal 100 to 500 times a second, calculating the average and

the range (maximum minus minimum) over 100 mS periods, and comparing these values to preset values to confirm proper operation and whether there was spray or not.

[00174] This method has the strong advantages of: low power consumption (less than 1 ma to the emitter); unaffected by stray light (visible light blocking on the detector); relatively resistant to digital noise or the 100 kHz piezo drive by the 100 Hz low-pass filter; the average signal level can be used to adjust the optical path for attenuation caused by drug deposits on the LED or detector; and simple hardware with a positive signal that is robustly measured.

[00175] This system also allows simple regulation of the optical signal strength by increasing power to the emitter should the average signal level decrease. Practically, this means using pulse width modulation of emitter current to regulate average emitter power. The pulses should be at a high rate, e.g., 100 kHz, so that this noise can be removed by the 100 Hz low pass filter. Nominal operation might use a 10% duty cycle of 10 mA to achieve and average current of 1 mA. This system would have the ability to increase the average current to 10 mA and correct for up to a factor of 10 attenuation by drug deposits.

[00176] In operation with the 950 nM emitter and detector having angles of +-20 degrees and spaced 10 mm apart. With 0.5 mA emitter power, a 10K collector resistor and 100 Hz low-pass filter, the average signal output is 2 volts and the peak to peak value of the alternating component is 4 mV without spray and 40 mV during spray. Without intending to be limited, in practice, there may be a transient large peak to peak value when the spray begins and ends as the bulk attenuation causes a large shift. The resistor sizing here is for continuous running of the emitter and not PWM.

[00177] Without limitation, the following are exemplary operational parameters for the in-line droplet delivery device of the disclosure.

1. Device turns ON when mouthpiece cover is opened.
    a) Left green LED always on and not blinking while device is ON and no error conditions. If error condition then the LED may be different (see sections after 5-9).
    b) Device must turn OFF (lights and all actions) when cap is closed
2. Breath actuation
    a) Device must be ready to breath actuate ¼ second after the mouthpiece is open
    b) Pressure sensor is read during voice, and dispense can begin during voice.

c) When dispense begins three green LEDs turn on. One second after dispense done chime sounds and three green LEDs blink for 9 seconds.

d) "Close the cap" begins 10 seconds after dispense is done.

e) Second breath actuation allowed 1 second (or more) after first dispense complete AND after pressure has dropped to very low level (first inhalation has ended). User can also press cap button (or close and then open cap) to reset device after first dispense completed to do a second breath-actuated dispense.

f) Device "wakes up" every 8 minutes to make sure cartridge is in place and cap is closed. User does not know that device has turned on to check cap.

g) Only four dispenses allowed each time cap is open (safety of children)

3. Dose Counter:

a) Is reset to 200 when a new cartridge is connected.

b) At completion of dispense the counter for that cartridge is incremented

c) Dose counter LED is on when the device is ON. Blue LED should blink when dose counter is less than 16 doses.

d) A method is needed to reset the dose counter for in-house testing (today it is cartridge with reset resistor)

4. Voice:

a) Voice starts about 0.25 second after cap is opened "exhale completely and then inhale deeply".

b) One second after dispense is done there is a chime and then "hold your breath 6 5 4 3 2 1 ". Then one second later "close the cap".

c) Volume control buttons can be adjusted any time the device is turned ON

d) Volume level is retained in memory

e) Volume level set to high when a new cartridge is connected

f) Voice will always have maximum volume for error messages.

5. Device left on:

a) If the device is left on for five or more seconds after the final part of "hold your breath", then the device enters the "turn off" state and remains in that state until it is turned OFF by closing the cap

b) In the "turn off" state, the device blinks the three red LEDs, makes a three harsh buzzes and voice says "close the cap" (full volume). The pattern

of three buzzes and voice repeats three times and then the device turns OFF. This pattern is done every eight minutes for three cycles. Then the pattern is done once every hour.

6. Cartridge missing:

a) When device is ON and cartridge is not detected in one second (either because cartridge is missing or not making good connection), device blinks red LED (middle). Harsh buzz and voice says "no cartridge". Sequence is repeated three times with three second pause between end of voice and next harsh buzz. Device then turns OFF until the cap is opened and the device then says "no cartridge" if there still is no cartridge.

b) When cartridge detected, left LED turns green and device begins "exhale completely" sequence.

7. Cartridge empty:

a) When there are sixteen or less doses remaining in cartridge, the left LED is yellow when the device turns ON. After ejection turn on three yellow LEDs and When there are 16, 8, 6, or 4 doses remaining, Voice says "replace cartridge soon" after "...5, 4, 3, 2, 1". When there are two doses or less voice says "replace cartridge".

b) When there are zero doses remaining in cartridge, all LEDs are red when device is ON. Voice says "Cartridge empty"

c) When a new cartridge is inserted the counter is reset.

d) When cartridge counter is 0, there are 10 "rescue" doses available. Device operates normally for "rescue" dose use.

8. Low battery:

a) When battery voltage during dispense drops below 3.1 volts, a "low battery" flag is set. The flag is a memory location.

b) When battery voltage drops below 2.9 volts 0.1 second before the end of a dispense, a "bad battery" flag is set

c) The "low battery" flag resets when the battery reads 4.5 volts or more when the device is ON. The "bad battery" flag resets when a battery voltage above 4.0 volts is detected when the device is turned ON.

d) When "low battery" flag is ON, the device blinks the yellow battery LED and voice says "replace batteries" when turned ON. Device will still dispense during a "low battery" flag.

e) When "bad battery" flag is ON, the device blinks the red battery LED and says "replace batteries before use". The device will blink all three LEDs and will not dispense during a "bad battery" condition.

9. Evaporation/Cartridge Expiry:

a) Cumulative time a cartridge is evaporating is measured by the total time the cartridge is not on the device after the cartridge is first detected by the device plus the total time the cap has not been closed while the cartridge is connected to the device.

b) When the evaporation time for a cartridge exceeds 75 hours the dose counter for the cartridge is set to 0 and all LEDs turn on with a steady red. Voice says "replace cartridge". Ten rescue doses are allowed when the dose counter is set to 0.

c) Cartridges with ID chips will store total evaporation time and total drug dispensed.

10. Communication with smart phone:

a) Smart phone communication can only begin when the device is ON. Communication ends when the device is turned OFF and current communication is completed. Communication does not occur during dispense.

[00178] The following examples demonstrate successful implementation of a device of the disclosure in the administration of an exemplary antibody composition (hIgG) to the lungs of a subject, and shows that systemic adsorption of the antibody was minimized.

EXAMPLES

EXAMPLE 1 – INHALATION STUDY

[00179] Exemplary devices of the disclosure were used to administer human IgG (hIgG) as an exemplary antibody composition in a dose dependent manner to the lungs of live Sprague-Dawley rats in a closed inhalation chamber. An exemplary device of the disclosure is continuously operated to ejected droplets including hIgG into the environment of a closed chamber housing subject live Sprague-Dawley rat subjects so as to achieve a desired hIgG concentration. The subject rats are allowed to inhale the ejected droplets including hIgG for a controlled period of time, such that the desired dosage is achieved. Once the desired dosage

is achieved, the subject rats are removed from the closed chamber. Dosage targets for subject rats are provided below:

[redacted] Dose Group	[redacted] Animal ID	Ear Mark	Tail Mark	[redacted] Animal ID	Pre-Exposure BW (g)	Drug	Target Dose Calculation
Control	101	1 LE punch	1 dot	1.1	247.0	DI H20	NA
Control	102	1 LE punch	2 dots	1.2	255.0	DI H20	NA
Control	103	1 LE punch	3 dots	1.3	251.0	DI H20	NA
IgG#1	021	2 RE punches	1 dot	2.1	267.0	IgG1	500 ug/mL
IgG#1	022	2 RE punches	2 dots	2.2	277.0	IgG1	500 ug/mL
IgG#1	023	2 RE punches	3 dots	2.3	266.0	IgG1	500 ug/mL
1	111	1 LE, 1 RE punch	1 dot	3.1	316.0	IgG	5 mg/mL
1	112	1 LE, 1 RE punch	2 dots	3.2	349.0	IgG	5 mg/mL
1	113	1 LE, 1 RE punch	3 dots	3.3	330.0	IgG	5 mg/mL
2	201	2 LE punches	1 dot	4.1	320.0	IgG	25 mg/mL
2	202	2 LE punches	2 dots	4.2	323.0	IgG	25 mg/mL
2	203	2 LE punches	3 dots	4.3	303.0	IgG	25 mg/mL

[00180] After a physical examination, rats were euthanized with isoflurane/CO_2. Blood was collected via caudal vena cava and 0.5 mL decanted into a 1.0 mL EDTA tube. Trachea and lungs were exposed and examined. Lungs were inflated with air via air-filled syringe and needle inserted into the trachea. Trachea was tied with string to maintain inflation. Lung pluck was immersed into 10% neutral buffered formalin for 24 hours.

[00181] Lungs were trimmed according to RENI criteria for inhalation studies (https://www.niehs.nih.gov/research/atniehs/labs/assets/docs/q_z/revised_guides_for_organ_sampling_and_trimming_in_rats_and_mice_508.pdf) and trachea was cut in cross sections. Tissues were routinely processed for paraffin embedment.

[00182] Five-micron lung and trachea sections were stained with H&E. Additional sections were subjected to anti-human IgG immunohistochemistry with DAB (stained/brown) chromogen indicating location of human IgG.

[00183] Tissues were scored to distribution and amount of bound antibody (referred to as IgG label) using a modified standard grading system whereby 0 = no significant IgG labeling, 1 = minimal scattered to diffuse IgG labeling, 2 = mild scattered to diffuse IgG labeling, 3 = moderate diffuse IgG labeling and 4 = marked diffuse IgG labeling. Regions of the lung examined included trachea, bronchus, proximal bronchioles on the left or right lobes, proximal alveoli on the left or right lobes, distal bronchioles on the left or right lobes and distal alveoli (adjacent to the pleura) on the left or right lobes (see **FIGS. 22A-22G**). A total score was calculated from the left and right lobe scores.

[00184] Histological and IHC Findings:

[00185] Several changes were noted in the lungs of all rats. Of these changes, inflammatory infiltrates are considered a notable finding. All the changes are described below.

- The presence of lymphocytic aggregates around the bronchiolar airways in rats is considered a normal anatomical finding, and was reported to verify the amount was consistent with that found in healthy rats.
- Collapse of the lung parenchyma is atelectasis, and can occur when air has evacuated the lung tissue during sample collection.
- Inflammatory cell infiltrates were noted when present as it reflects a response to some kind of lung injury. Inflammatory cells are carried to the lung via blood vessels or may be resident and activated when the tissue is injured.
- Blood leakage or hemorrhage occurs from rupture of small capillaries and in this study was considered a consequence of postmortem sample collection and not associated with hIgG aerosolization.

[00186] No notable histologic findings or hIgG labeling was observed in any region or lung lobe in Group 1 dosed with deionized water.

[00187] In lung samples from Group 2, hIgG labeling was minimal to mild and scattered to diffuse in proximal bronchioles and alveolar sacs. Labeling intensity and distribution in general was decreased in distal bronchioles and alveoli. The level of IgG label on the surface of the trachea was generally less than that observed on the surface of bronchioles, a possible result of ciliary clearance prior to sample collection.

[00188] In Group 3, hIgG labeling in lung parenchyma was minimal to mild and better distributed to distal portions of the lung than the labeling observed in Group 2. Tracheal labeling in this group was also less than that observed in bronchioles or alveoli, a possible result of ciliary clearance prior to sample collection. In the lungs of one rat were minimal numbers of lymphocytes that egressed from blood vessels into perivascular interstitial spaces. This inflammatory response may be related to either duration of hIgG exposure (longer as compared to that of Group 2) or to concentration of hIgG (higher in Group 3 as compared to that of Group 2) or both.

[00189] The distribution and level of IgG labeling in Group 4 was mild to moderate in proximal and distal lung tissues of both left and right lung lobes. Distribution of IgG to the distal alveoli was more consistent than in Groups 2 or 3 and was essentially equal between

left and right lung lobes. Tracheal labeling in this group was also less than that observed in bronchioles or alveoli, a possible result of ciliary clearance prior to sample collection. In lungs from all rats were mild numbers of lymphocytes egressing from blood vessels into the interstitial spaces around blood vessels. This inflammatory response may be related to either duration of hIgG exposure (longer as compared to that of Group 2) or to concentration of hIgG (10 fold higher in this Group as compared to that of Group 2) or both.

[00190] **FIG. 22A** illustrates an annotated photomicrograph to show the location of brown IHC label on deposits of hIgG. The figure illustrates lung section from Group 2 rat 2.1, probed with anti-human IgG and visualized with DAB chromogen and photographed with 20x magnification. Brown label of human IgG deposited on ciliated epithelium on bronchioles is illustrated with solid arrows, and deposits on pneumocytes lining alveoli are illustrated with dashed arrows.

[00191] **FIGS. 22B** and **22C** illustrate lung sections probed with anti-human IgG from rat 2.1, probed with anti-human IgG (500 μg/mL IgG) and photographed with 20x magnification. **FIG. 22B** shows distal alveoli with a grading score 1, while **FIG. 22C** shows proximal bronchiole with a grading score 2.

[00192] **FIGS. 22D** and **22E** illustrate lung sections probed with anti-human IgG from rat 3.1, probed with anti-human IgG (5 mg/mL IgG) and photographed with 20x magnification. **FIG. 22D** shows distal alveoli with a grading score 1.5, while **FIG. 22C** shows distal bronchiole with a grading score 2.

[00193] **FIGS. 22F** and **22G** illustrate lung sections probed with anti-human IgG from rat 4.2, probed with anti-human IgG (25 mg/mL IgG) and photographed with 20x magnification. **FIG. 22F** shows distal alveoli with a grading score 3, while **FIG. 22G** shows distal bronchiole with a grading score 3.

[00194] Plasma hIgG Results

[00195] Plasma from rats in all Groups were tested in two replicates by a micro-bead based IgG-capture assay using the Milliplex MAP kit (EMD Millipore, HGAMMAG-301K). Assay validation was performed with kit controls, and tests were performed according to manufacturer's recommendations.

[00196] In samples from most rats in all Groups, no hIgG was detectable. That is, most all samples produced results below the limit of detection of the assay for all hIgG isotypes – IgG1, igG2, IgG3 and IgG4. One plasma sample in each of Group 3 and Group 4 gave low hIgG1 values that did not replicate. One plasma sample collected shortly after aerosolization in Group 4 had low IgG2, IgG3 and IgG4 values, but no result IgG1 which is the most

abundant isotype in the dose solution. Given the lack of repeatability and isotype distribution in the samples with non-zero results, it is not possible to conclude that appreciable hIgG was absorbed post-aerosolization.

[00197] Concentration of hIgG in Dose and Syringe Wash Samples

[00198] Samples of the dose material for Groups 3 and 4 (5mg/mL and 25mg/mL) and syringe washes collected at 1 and 2 hrs from each aerosolization experiment were submitted to assess concentration of hIgG, and were tested with the same kit as used for the plasma samples. Dose and wash samples were run at 3 dilutions (1:2500, 1:5000 and 1:10,000) and replicated twice. Total hIgG for the dose samples was calculated to be 15.67 mg/mL for Group 3 (5 mg/mL) and 90.48 mg/mL for Group 4 (25mg/mL). IgG1 concentration of the IgG1 isotype for the dose samples was approximately 6 mg/mL for Group 3 and 35 mg/mL for Group 4.

[00199] Results are shown in the tables below.

Table A: Summary of Histological and hIgG IHC Evaluation

	Gp 1: Control		Gp 2: 10mg/mL IgG		Gp 3: 5 mg/mL IgG	
	# Changes	Average Score	# Changes	Average Score	# Changes	Average Score
Lungs						
H&E						
Lymphoid aggregates, peribronchiolar	2	2.0	2	2.0	3	2.0
Atelectasis	2	1.5	2	1.5	1	2.0
Infiltrates, mast cell/lymphocytes	0		2	1.5	1	1.0
Hemorrhage	1	1.0	1	1.0	1	1.0
IgG Label						
Trachea	0		3	0.8	3	0.8
Bronchus	0		1	2.0	0	
Bronchioles LL - proximal	0		3	1.7	3	1.5
Bronchioles LL - distal	0		3	0.8	3	1.2
Bronchioles RL - proximal	0		3	2.0	3	2.0
Bronchioles RL- distal	0		3	1.0	3	1.3
Alveoli LL - proximal	0		3	1.3	3	1.7
Alveoli LL - distal	0		3	0.8	3	1.3
Alveoli RL- proximal	0		3	2.0	3	2.0
Alveoli RL - distal	0		3	0.8	3	1.0
Total Tissues Per Group	30		28		27	
Total IHC Tissues Labeled	0		28		27	
Total IHC Score	0.0		36.0		38.5	
Average Score/Sample	0.0		1.3		1.4	

	Gp 4: 25 mg/mL IgG	
	# Changes	Average Score
Lungs		
H&E		
Lymphoid aggregates, peribronchiolar	3	6.0
Atelectasis	1	2.5
Infiltrates, mast cell/lymphocytes	2	4.0
Hemorrhage	1	1.0
IgG Label		
Trachea	2	3.0
Bronchus	1	1.0
Bronchioles LL - proximal	3	9.0
Bronchioles LL - distal	3	7.0
Bronchioles RL - proximal	3	8.5
Bronchioles RL- distal	3	7.0
Alveoli LL - proximal	3	9.0
Alveoli LL - distal	3	7.0
Alveoli RL- proximal	3	8.5
Alveoli RL - distal	3	8.0
Total Tissues Per Group	28	
Total IHC Tissues Labeled	27	
Total IHC Score	68.0	
Average Score/Sample	2.4	

Table B: Individual Animal Histological Findings

Group 1: Control	1.1	1.2	1.3	Total Score	# Changes	Ave Score	Notes:
Lungs							
H&E							
Lymphoid aggregates, peribronchiolar	2	2	0	4.0	2	2.00	
Atelectasis	1	2	0	3.0	2	1.50	
Infiltrates, mast cell/lymphocytes	0	0	0	0.0	0		
Hemorrhage	0	0	1	1.0	1	1.00	
IgG Label							
Trachea	0	0	0	0.0	0		
Bronchus	0	NP	NP	0.0	0		
Bronchioles LL - proximal	0	0	0	0.0	0		
Bronchioles LL - distal	0	0	0	0.0	0		
Bronchioles RL - proximal	0	0	0	0.0	0		
Bronchioles RL- distal	0	0	0	0.0	0		
Alveoli LL - proximal	0	0	0	0.0	0		
Alveoli LL - distal	0	0	0	0.0	0		
Alveoli RL- proximal	0	0	0	0.0	0		
Alveoli RL - distal	0	0	0	0.0	0		
Artifact/Incidental	1	0	1	2.0	2	1.00	epithelial cells in trachea
IHC Scores per animal (- artifact):	3	4	1	8.0			

Group 2: 10mg/mL hIgG	2.1	2.2	2.3	Total Score	# Changes	Ave Score	Notes:
Lungs							
H&E							
Lymphoid aggregates, peribronchiolar	2	2	0	4.0	2	2.00	
Atelectasis	2	1	0	3.0	2	1.50	
Infiltrates, mast cell/lymphocytes	2	0	1	3.0	2	1.50	perivascular
Hemorrhage	0	1	0	1.0	1	1.00	
IgG Label							
Trachea	1	0.5	1	2.5	3	0.83	
Bronchus	NP	2	NP	2.0	1	2.00	
Bronchioles LL - proximal	2	1	2	5.0	3	1.67	
Bronchioles LL - distal	1	1	0.5	2.5	3	0.83	
Bronchioles RL - proximal	2	2	2	6.0	3	2.00	
Bronchioles RL- distal	1	1	1	3.0	3	1.00	
Alveoli LL - proximal	2	1	1	4.0	3	1.33	
Alveoli LL - distal	1.5	0.5	0.5	2.5	3	0.83	mild - caudal region
Alveoli RL- proximal	2	2	2	6.0	3	2.00	caudal/accessory lobes
Alveoli RL - distal	0.5	1	1	2.5	3	0.83	
Artifact/incidental	0	0	0	0	0		
IHC Scores per animal (- artifact):	13	12	11	36.0			

NP = tissue not present

Group 3: 5 mg/mL hIgG	3.1	3.2	3.3	Total Score	# Changes	Ave Score	Notes:
Lungs							
H&E							
Lymphoid aggregates, peribronchiolar	2	2	2	6.0	3	2.00	
Atelectasis	0	0	2	2.0	1	2.00	
Infiltrates, mast cell/lymphocytes	1	0	0	1.0	1	1.00	
Hemorrhage	1	0	0	1.0	1	1.00	
IgG Label							
Trachea	0.5	1	1	2.5	3	0.83	
Bronchus	NP	NP	NP				
Bronchioles LL - proximal	2	2	0.5	4.5	3	1.50	
Bronchioles LL - distal	1	1.5	1	3.5	3	1.17	
Bronchioles RL - proximal	2	2	2	6.0	3	2.00	
Bronchioles RL- distal	2	1	1	4.0	3	1.33	
Alveoli LL - proximal	2	2	1	5.0	3	1.67	
Alveoli LL - distal	1.5	1.5	1	4.0	3	1.33	
Alveoli RL- proximal	2	2	2	6.0	3	2.00	
Alveoli RL - distal	1	1	1	3.0	3	1.00	
Artifact/Incidental	0	0	0	0	0		
IHC Scores per animal (- artifact):	14	14	10.5	38.5			

Group 4: 25mg/mL hIgG	4.1	4.2	4.3	Total Score	# Changes	Ave Score	Notes:
Lungs							
H&E							
Lymphoid aggregates, peribronchiolar	2	2	2	6.0	3	2.00	
Atelectasis/underinflation	0	0	2.5	2.5	1	2.50	rat 3.3
Infiltrates, mast cell/lymphocytes	0	2	2	4.0	2	2.00	
Hemorrhage	1	0	0	1.0	1	1.00	
IgG Label							
Trachea	2	1	0	3.0	2	1.50	
Bronchus	1	NP	NP	1.0	1	1.00	
Bronchioles LL - proximal	3	3	3	9.0	3	3.00	
Bronchioles LL - distal	2	3	2	7.0	3	2.33	
Bronchioles RL - proximal	2.5	3	3	8.5	3	2.83	
Bronchioles RL - distal	2	3	2	7.0	3	2.33	
Alveoli LL - proximal	3	3	3	9.0	3	3.00	
Alveoli LL - distal	2	3	2	7.0	3	2.33	
Alveoli RL - proximal	2.5	3	3	8.5	3	2.83	
Alveoli RL - distal	2	3	3	8.0	3	2.67	
Artifact/Incidental	0	0	0	0	0		
IHC Scores per animal (- artifact):	22	25	21	68.0			

NP = tissue not present

Table C. Plasma hIgG Concentration

	hIgG1 [ng/mL]		hIgG2 [ng/mL]		hIgG3 [ng/mL]		hIgG4 [ng/mL]	
Sample ID	Replicate 1	Replicate 2	Replicate 1	Replicate 2	Replicate 1	Replicate 2	Replicate 1	Replicate 2
1.1 t0 control	< 14	< 14	< 41	< 41	< 0.2	< 0.2	< 0.4	< 0.4
1.2 t0 control	< 14	< 14	< 41	< 41	< 0.2	< 0.2	< 0.4	< 0.4
1.3 t0 control	< 14	< 14	< 41	< 41	< 0.2	< 0.2	< 0.4	< 0.4
1.1 tpm control	< 14	< 14	< 41	< 41	< 0.2	< 0.2	< 0.4	< 0.4
1.2 tpm control	< 14	< 14	< 41	< 41	< 0.2	< 0.2	< 0.4	< 0.4
1.3 tpm control	< 14	< 14	< 41	< 41	< 0.2	< 0.2	< 0.4	< 0.4
2.1 t0 HIgG	< 14	< 14	< 41	< 41	< 0.2	< 0.2	< 0.4	< 0.4
2.2 t0 HIgG	< 14	< 14	< 41	< 41	< 0.2	< 0.2	< 0.4	< 0.4
2.3 t0 HIgG	< 14	< 14	< 41	< 41	< 0.2	< 0.2	< 0.4	< 0.4
2.1 tpm HIgG	< 14	< 14	< 41	< 41	< 0.2	< 0.2	< 0.4	< 0.4
2.2 tpm HIgG	< 14	< 14	< 41	< 41	< 0.2	< 0.2	< 0.4	< 0.4
2.3 tpm HIgG	< 14	< 14	< 41	< 41	< 0.2	< 0.2	< 0.4	< 0.4
3.1 t0 IgG-S	< 14	< 14	< 41	< 41	< 0.2	< 0.2	< 0.4	< 0.4
3.2 t0 IgG-S	< 14	< 14	< 41	< 41	< 0.2	< 0.2	< 0.4	< 0.4
3.3 t0 IgG-S	< 14	< 14	< 41	< 41	< 0.2	< 0.2	< 0.4	< 0.4
3.1 tpm IgG-S	< 14	34.2331	< 41	< 41	< 0.2	< 0.2	< 0.4	< 0.4
3.2 tpm IgG-S	< 14	< 14	< 41	< 41	< 0.2	< 0.2	< 0.4	< 0.4
3.3 tpm IgG-S	< 14	< 14	< 41	< 41	< 0.2	< 0.2	< 0.4	< 0.4
4.1 t0 IgG-2S	< 14	< 14	< 41	< 41	< 0.2	< 0.2	< 0.4	< 0.4
4.2 t0 IgG-2S	< 14	< 14	< 41	< 41	< 0.2	< 0.2	< 0.4	< 0.4
4.3 t0 IgG-2S	< 14	< 14	43.3757	< 41	3.9913	4.1581	3.3549	3.2477
4.1 tpm IgG-2S	< 14	< 14	< 41	< 41	< 0.2	< 0.2	< 0.4	< 0.4
4.2 tpm IgG-2S	< 14	< 14	< 41	< 41	< 0.2	< 0.2	< 0.4	< 0.4
4.3 tpm IgG-2S	16.2793	< 14	< 41	< 41	< 0.2	< 0.2	< 0.4	< 0.4

t0 = time 1 post-nebulization
tpm = time 2 at post-mortem exam

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Assay QC	hIgG1 (ng/mL)	hIgG2 (ng/mL)	hIgG3 (ng/mL)	hIgG4 (ng/mL)
Control 1	439.47	3210.30	7.61	27.80
Control 2	426.29	3120.11	7.29	27.15
Expected	369-767	2235-4642	7.3-15	26-54
R^2	0.993	0.996	0.995	0.998

Table D: hIgG Concentrations in Dose Solution and Filter Washes

		hIgG1 (ng/mL)			hIgG2 (ng/mL)		
Vial Label	Dilution	Replicate 1	Replicate 2	Mean	Replicate 1	Replicate 2	Mean
25 mg/mL dose (2500 dilution)	2500	1612.25	1520.94	1566.60	2057.56	2122.00	2089.78
25 mg/mL dose (5000 dilution)	5000	783.82	681.38	732.60	1071.29	961.15	1016.22
25 mg/mL dose (10000 dilution)	10000	370.45	329.18	349.81	497.83	439.85	468.84
5 mg/mL dose (500 dilution)	500	1373.35	1373.35	1373.35	1956.16	1775.04	1865.60
5 mg/mL dose (1000 dilution)	1000	631.23	725.05	678.14	935.87	932.26	934.06
5 mg/mL dose (2000 dilution)	2000	302.80	288.75	295.77	474.77	368.50	421.64
Exp. 1 S1-1hr	2	180.04	175.81	177.93	497.83	533.06	515.44
Exp. 2 S1-1hr	2	840.76	760.65	800.70	1746.24	1672.84	1709.54
Exp. 2 S2-1hr	2	140.98	172.25	156.62	410.39	418.29	414.34
Exp. 2 S2-2hr	2	647.23	809.26	728.25	1800.08	2192.22	1996.15

		hIgG3 (ng/mL)			hIgG4 (ng/mL)		
Vial Label	Dilution	Replicate 1	Replicate 2	Mean	Replicate 1	Replicate 2	Mean
25 mg/mL dose (2500 dilution)	2500	> 150	> 150	#DIV/0!	> 300	> 300	#DIV/0!
25 mg/mL dose (5000 dilution)	5000	> 150	> 150	#DIV/0!	73.09	75.40	74.25
25 mg/mL dose (10000 dilution)	10000	61.21	53.17	57.19	29.97	27.96	28.96
5 mg/mL dose (500 dilution)	500	> 150	> 150	#DIV/0!	> 300	> 300	#DIV/0!
5 mg/mL dose (1000 dilution)	1000	> 150	> 150	#DIV/0!	68.95	73.18	71.06
5 mg/mL dose (2000 dilution)	2000	45.52	39.40	42.46	24.49	23.12	23.81
Exp. 1 S1-1hr	2	4.43	4.35	4.39	10.73	10.32	10.53
Exp. 2 S1-1hr	2	28.55	27.51	28.03	101.61	92.61	97.11
Exp. 2 S2-1hr	2	3.91	3.75	3.83	6.73	6.86	6.79
Exp. 2 S2-2hr	2	27.19	38.05	32.62	95.06	192.48	143.77

		Summary of hIgG (mg/mL)				Total IgG
Vial Label	Dilution	hIgG1	hIgG2	hIgG3	hIgG4	(mg/mL)
25 mg/mL dose (2500 dilution)	2500	39.16	52.24	#DIV/0!	#DIV/0!	91.41 *
25 mg/mL dose (5000 dilution)	5000	36.63	50.81	#DIV/0!	3.71	87.44 *
25 mg/mL dose (10000 dilution)	10000	34.98	46.88	5.72	2.90	90.48
5 mg/mL dose (500 dilution)	500	6.87	9.33	#DIV/0!	#DIV/0!	16.19 *
5 mg/mL dose (1000 dilution)	1000	6.78	9.34	#DIV/0!	0.71	16.12 *
5 mg/mL dose (2000 dilution)	2000	5.92	8.43	0.85	0.48	15.67
Exp. 1 S1-1hr	2	0.0036	0.0103	0.0001	0.0002	0.0142
Exp. 2 S1-1hr	2	0.0160	0.0342	0.0006	0.0019	0.0527
Exp. 2 S2-1hr	2	0.0031	0.0083	0.0001	0.0001	0.0116
Exp. 2 S2-2hr	2	0.0146	0.0399	0.0007	0.0029	0.0580

* not all isotypes included - values out of range

[00200] As demonstrated, it has been found that exemplary antibody compositions (hIgG) can be successfully delivered in a dose dependent manner to the lungs of a subject via inhalation using a device of the disclosure, and can be distributed in proximal and distal lung tissues, including alveoli, bronchioles, and trachea. In addition, it has been found that exemplary antibody compositions (hIgG) can be successfully delivered locally to the lungs via inhalation using a device of the disclosure in a manner that minimizes systemic uptake.

EXAMPLE 2 –SYSTEMIC UPTAKE STUDY

[00201] In a similar method as described with reference to Example 1, hIgG was administered to subject Sprague-Dawley rats in a dose dependent manner in a closed chamber using exemplary devices of the disclosure to investigate systemic uptake of hIgG following pulmonary delivery. Dosage targets for subject rats are provided below:

Dose Group	ARE Animal ID	Drug	Target Dose Calculation
aerosol	011	hIgG	25 mg/mL
aerosol	012	hIgG	25 mg/mL
aerosol	013	hIgG	25 mg/mL
IP	111	hIgG	100ug.mL
IP	112	hIgG	100ug.mL
IP	111	hIgG	100ug.mL

[00202] For subject rats 011 and 013, blood samples are drawn at time 0 (the conclusion of droplet ejection of hIgG) and time 24 hours post-ejection. For subject rats 111 and 112, blood samples are drawn at time 0, at 2 hour and at 4 hour intervals.

[00203] Plasma hIgG Results

[00204] Plasma from subject rats in both Groups (aerosol test group and IP control group) were tested in two replicates at a 1:2 dilution by a micro-bead based IgG capture assay using the Milliplex MAP kit (EMD Millipore, HGAMMAG-301K). Assay validation was performed with kit controls, and tests were performed according to manufacturer's recommendations.

[00205] In samples from rats in both aerosol test and IP control dosed Groups, hIgG was detectable. The exception was the time 0 samples collected from the two rats dosed by intraperitoneal injection. In the rats dosed by aerosol, levels of the most abundant isotype of hIgG, IgG1, increased 3 to 5-fold at 24 hours as compared to the time 0 levels. And the levels detected at 24 hrs post-aerosol dosing compared favorably to those detected in the plasma of rats dosed with hIgG by injection.

[00206] Concentration of hIgG in Dose and Syringe Wash Samples

[00207] Samples of the dose material (200ug/mL) and syringe washes collected at 45, 80 and 120 minutes during the dosing experiment were submitted to assess concentration of hIgG. These samples were tested with the same kit as used for the plasma samples.

[00208] Dose and wash samples were run at 2 or 3 dilutions based on the expected concentration of hIgG and replicated twice. Total hIgG for the dose sample was calculated to be about 100 ug/mL. Concentration of hIgG in the wash solutions was from 14-20 mg/mL.

[00209] Results are shown in the tables below.

Table E: Dose and Plasma IgG Individual Replicate Data

		hIgG1 (ng/mL)			hIgG2 (ng/mL)		
Vial Label	Dilution	Replicate 1	Replicate 2	Mean	Replicate 1	Replicate 2	Mean
200 vial (20 dilution)	20	2921.5857	2719.5664	2820.58	2725.3191	2573.3428	2649.33
200 vial (40 dilution)	40	1184.986	1305.1259	1245.06	1079.9799	1079.9799	1079.98
200 vial (80 dilution)	80	558.18783	509.96475	534.08	491.42171	366.31165	428.87
T-45 (10 dilution)	10	557.19851	609.91582	583.56	672.78688	827.0045	749.90
T-45 (20 dilution)	20	281.57834	348.07638	314.83	236.23033	417.16651	326.70
T-80 (10 dilution)	10	861.37514	712.90204	787.14	924.00363	870.50631	897.25
T-80 (20 dilution)	20	298.04272	261.61119	279.83	376.73421	471.61596	424.18
T- 120 (10 dilution)	10	828.09044	844.71279	836.40	1020.5333	1015.598	1018.07
T-120 (20 dilution)	20	371.54339	277.93496	324.74	394.65956	367.79903	381.23
011 1hr	2	31.411433	11.425103	21.42	< 41	< 41	< 41
012 1hr	2	32.817371	< 14	32.82	< 41	< 41	< 41
013 1hr	2	13.940571	9.5805212	11.76	< 41	< 41	< 41
011 24hr	2	58.431197	71.429369	64.93	< 41	< 41	< 41
012 24hr	2	95.855006	123.53132	109.69	< 41	< 41	< 41
013 24hr	2	27.239653	88.676729	57.96	< 41	< 41	< 41
121 0hr	2	*	*	*	< 41	< 41	< 41
122 0hr	2	< 14	< 14	< 14	< 41	< 41	< 41
121 2hr	2	88.676729	71.429369	80.05	< 41	< 41	< 41
122 2hr	2	45.039579	88.676729	66.86	< 41	< 41	< 41
121 4hr	2	62.221455	72.978465	67.60	< 41	< 41	< 41
122 4hr	2	105.52648	116.94508	111.24	< 41	< 41	< 41

* - value being repeated

		hIgG3 (ng/mL)			hIgG4 (ng/mL)		
Vial Label	Dilution	Replicate 1	Replicate 2	Mean	Replicate 1	Replicate 2	Mean
200 vial (20 dilution)	20	> 150	> 150	> 150	> 300	> 300	> 300
200 vial (40 dilution)	40	> 150	> 150	> 150	> 300	> 300	> 300
200 vial (80 dilution)	80	> 150	> 150	> 150	61.684051	62.326814	62.01
T-45 (10 dilution)	10	64.416089	54.136445	59.28	81.028787	81.290015	81.13
T-45 (20 dilution)	20	22.306611	22.88115	22.59	39.178267	41.193547	40.19
T-80 (10 dilution)	10	> 150	> 150	> 150	131.35944	115.68015	123.62
T-80 (20 dilution)	20	27.223233	28.843316	28.03	46.478846	46.584525	46.53
T- 120 (10 dilution)	10	> 150	> 150	> 150	134.56948	123.17705	128.87
T-120 (20 dilution)	20	41.568871	40.03365	40.80	48.056399	47.123853	47.59
011 1hr	2	0.2869918	0.1980601	0.24	< 0.4	< 0.4	< 0.4
012 1hr	2	0.3866998	0.341946	0.36	< 0.4	< 0.4	< 0.4
013 1hr	2	0.232203	0.1878345	0.21	< 0.4	< 0.4	< 0.4
011 24hr	2	1.6062334	1.3702826	1.49	< 0.4	< 0.4	< 0.4
012 24hr	2	2.3921783	2.5059362	2.45	0.8162507	1.0311745	0.92
013 24hr	2	1.9135285	2.1366373	2.03	< 0.4	< 0.4	< 0.4
121 0hr	2	< 0.2	< 0.2	< 0.2	< 0.4	< 0.4	< 0.4
122 0hr	2	< 0.2	< 0.2	< 0.2	< 0.4	< 0.4	< 0.4
121 2hr	2	3.3625604	3.2122208	3.29	3.4440835	3.4001874	3.42
122 2hr	2	1.366766	1.4652888	1.42	1.1253248	0.9253646	1.03
121 4hr	2	2.6269249	2.7836806	2.71	2.1825956	2.5215184	2.35
122 4hr	2	8.1666791	8.1779369	8.17	8.8932991	8.5383399	8.72

Table F: Dose and Plasma IgG Summary Data

		hIgG (µg/mL)				Total IgG	Notes
Vial Label	Dilution	hIgG1	hIgG2	hIgG3	hIgG4	(µg/mL)	
200 vial (20 dilution)	20	56.41	52.99	> 150	> 300	109.40	1
200 vial (40 dilution)	40	49.80	43.20	> 150	> 300	93.00	1
200 vial (80 dilution)	80	42.73	34.31	> 150	4.96	82.00	
T-45 (10 dilution)	10	5.84	7.50	0.59	0.81	14.74	
T-45 (20 dilution)	20	6.30	6.53	0.45	0.80	14.09	
T-80 (10 dilution)	10	7.87	8.97	> 150	1.24	18.08	2
T-80 (20 dilution)	20	5.60	8.48	0.56	0.93	15.57	
T- 120 (10 dilution)	10	8.36	10.18	> 150	1.29	19.83	2
T-120 (20 dilution)	20	6.49	7.62	0.82	0.95	15.89	
011 1hr	2	0.042837	0.000000	0.000485	0.000000	0.0433	
012 1hr	2	0.065635	0.000000	0.000729	0.000000	0.0664	
013 1hr	2	0.023521	0.000000	0.000420	0.000000	0.0239	
011 24hr	2	0.129861	0.000000	0.002977	0.000000	0.1328	
012 24hr	2	0.219386	0.000000	0.004898	0.001847	0.2261	
013 24hr	2	0.115916	0.000000	0.004050	0.000000	0.1200	
121 0hr	2	*	0.000000	0.000000	0.000000	0.0000	
122 0hr	2	0.000000	0.000000	0.000000	0.000000	0.0000	
121 2hr	2	0.160106	0.000000	0.006575	0.006844	0.1735	
122 2hr	2	0.133716	0.000000	0.002832	0.002051	0.1386	
121 4hr	2	0.135200	0.000000	0.005411	0.004704	0.1453	
122 4hr	2	0.222472	0.000000	0.016345	0.017432	0.2562	

* - value being repeated

[1] Total IgG does not include IgG3 or IgG4

[2] Total IgG does not include IgG3

[00210] In this regard, in accordance with aspects of the disclosure, substantially larger dosages of active agent can be locally delivered to the lungs via inhalation in a manner that results in minimal systemic exposure to and uptake of the active agent. For instance, similar systemic plasma concentrations of an exemplary antibody are observed in subjects when dosed via inhalation at a dosage amount 250 times greater than when dosed via oral, systemic or parenteral route.

WHAT IS CLAIMED:

1. A method for treating pulmonary cancer in a subject in need thereof by delivering a therapeutic agent as an ejected stream of droplets in a respirable range to the pulmonary system of the subject, the method comprising:

(a) generating an ejected stream of droplets comprising a cancer therapeutic via a breath actuated piezoelectric actuated droplet delivery device, wherein at least about 50% of the ejected stream of droplets have an average ejected droplet diameter of less than about 6 μm; and

(b) delivering the ejected stream of droplets to the pulmonary system of the subject such that at least about 50% of the mass of the ejected stream of droplets is delivered in a respirable range to the pulmonary system of a subject during use to thereby treat the pulmonary cancer.

2. The method of claim 1, wherein the cancer therapeutic comprises a chemotherapeutic agent, immune checkpoint inhibitor, or combinations thereof.

3. The method of claim 2, wherein the chemotherapeutic agent is selected from the group consisting of paclitaxel, doxorubicin, gemcitabine, 9-nitrocamptothecin, 5-azacytidine, celecoxib, 5-fluorouracil, cisplatin, carboplatin, oxaliplatin, nedaplatin, picoplatin, and combinations thereof.

4. The method of claim 2, wherein the immune checkpoint inhibitor is selected from the group consisting of CTLA-4 inhibitors, PD-1 inhibitors, PD-L1 inhibitors, and combinations thereof.

5. The method of claim 2, wherein the immune checkpoint inhibitor is selected from the group consisting of Pembrolizumab, Nivolumab, Atezolizumab, Avelumab, Durvalumab, and Ipilimumab, and combinations thereof.

6. The method of claim 1, wherein the breath actuated piezoelectric actuated droplet delivery device is an in-line droplet delivery device comprising:

a housing configured in a substantially in-line orientation;

a mouthpiece positioned at an airflow exit of the device;

an air inlet flow element positioned in the airflow at an airflow entrance of the device;

a reservoir disposed within or in fluid communication with the housing for receiving a volume of fluid;

an electronically actuated ejector mechanism in fluid communication with the reservoir and configured to generate the ejected stream of droplets;

at least one differential pressure sensor positioned within the housing, the at least one differential pressure sensor configured to activate the ejector mechanism upon sensing a pre-determined pressure change within the mouthpiece to thereby generate the ejected stream of droplets;

the ejector mechanism comprising a piezoelectric actuator and an aperture plate, the aperture plate having a plurality of openings formed through its thickness and the piezoelectric actuator operable to oscillate the aperture plate at a frequency to thereby generate the ejected stream of droplets;

wherein the housing, air inlet flow element, and mouthpiece are configured to facilitate non-turbulent airflow across an exit side of the aperture plate and to provide sufficient airflow through the housing during use; and

wherein the ejector mechanism is configured to generate the ejected stream of droplets wherein at least about 50% of the droplets have an average ejected droplet diameter of less than about 6 microns, such that at least about 50% of the mass of the ejected stream of droplets is delivered in a respirable range to the pulmonary system of the subject during use.

7. The method of claim 6, wherein the housing and ejector mechanism are oriented such that the exit side of the aperture plate is perpendicular to the direction of airflow and the stream of droplets is ejected in parallel to the direction of airflow.

8. The method of claim 6, wherein the housing and ejector mechanism are oriented such that the exit side of the aperture plate is parallel to the direction of airflow and the stream of droplets is ejected substantially perpendicularly to the direction of airflow such that the ejected stream of droplets is directed through the housing at an approximate 90 degree change of trajectory prior to expulsion from the housing.

9. The method of claim 6, wherein the air inlet flow element is positioned within the mouthpiece.

10. The method of claim 9, wherein the air inlet flow element is positioned behind the exit side of the aperture plate along the direction of airflow.

11. The method of claim 9, wherein the air inlet flow element is positioned in-line or in front of the exit side of the aperture plate along the direction of airflow.

12. The method of claim 6, wherein the air inlet flow element comprises one or more openings formed there through and configured to increase or decrease internal pressure resistance within the droplet delivery device during use.

13. The method of claim 12, wherein the air inlet flow element comprises an array of one or more openings.

14. The method of claim 13, wherein the air inlet flow element comprises one or more baffles.

15. The method of claim 14, wherein the one or more baffles comprise one or more airflow openings.

16. The method of claim 6, wherein the reservoir comprises an internal flexible membrane separating two internal volumes, a first background pressure fluid volume and a second drug volume received by the drug reservoir.

17. The method of claim 6, wherein the aperture plate is composed of a material selected from the group consisting of poly ether ether ketone (PEEK), polyimide, polyetherimide, polyvinylidine fluoride (PVDF), ultra-high molecular weight polyethylene (UHMWPE), nickel, nickel-cobalt, nickel-palladium, palladium, platinum, metal alloys thereof, and combinations thereof.

18. The method of claim 6, wherein the mouthpiece is removably coupled with the device.

19. The method of claim 6, wherein the reservoir is removably coupled with the housing.

20. The method of claim 6, wherein the reservoir is coupled to the ejector mechanism to form a combination reservoir/ejector mechanism module, and the combination reservoir/ejector mechanism module is removably coupled with the housing.

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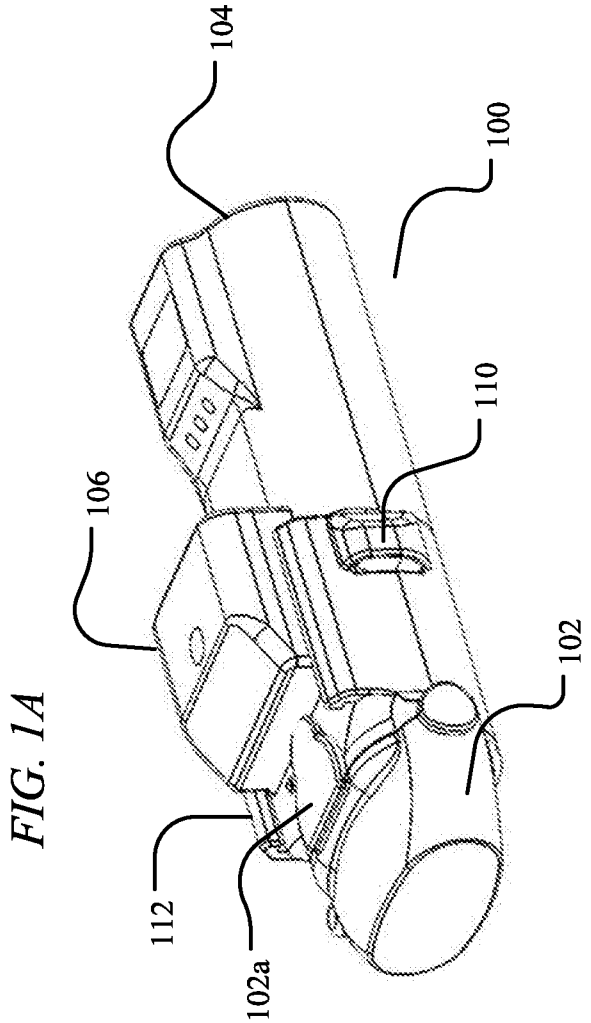


FIG. 1A

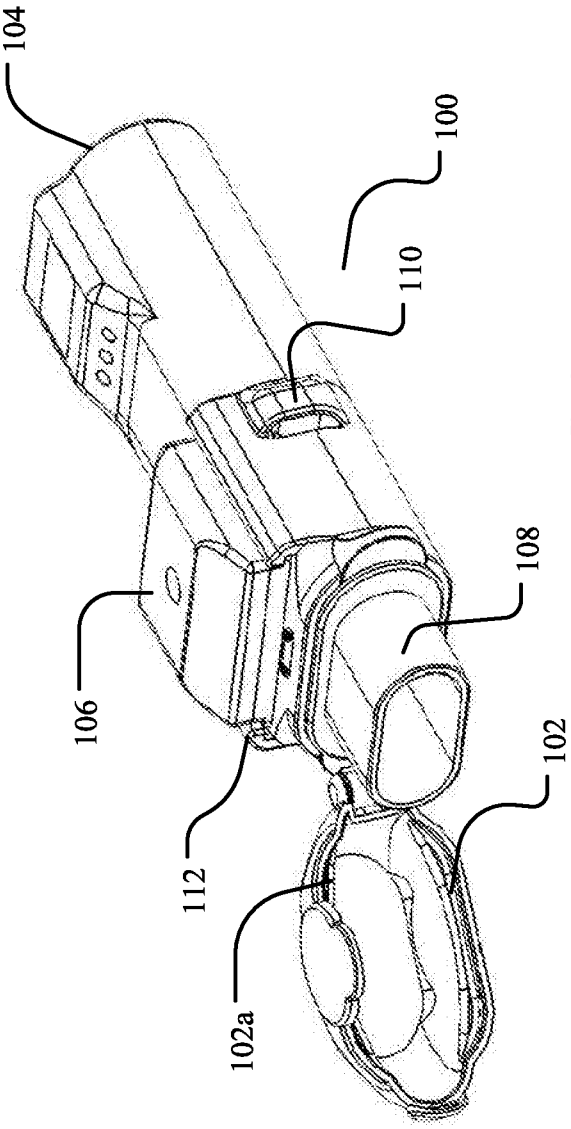


FIG. 1B

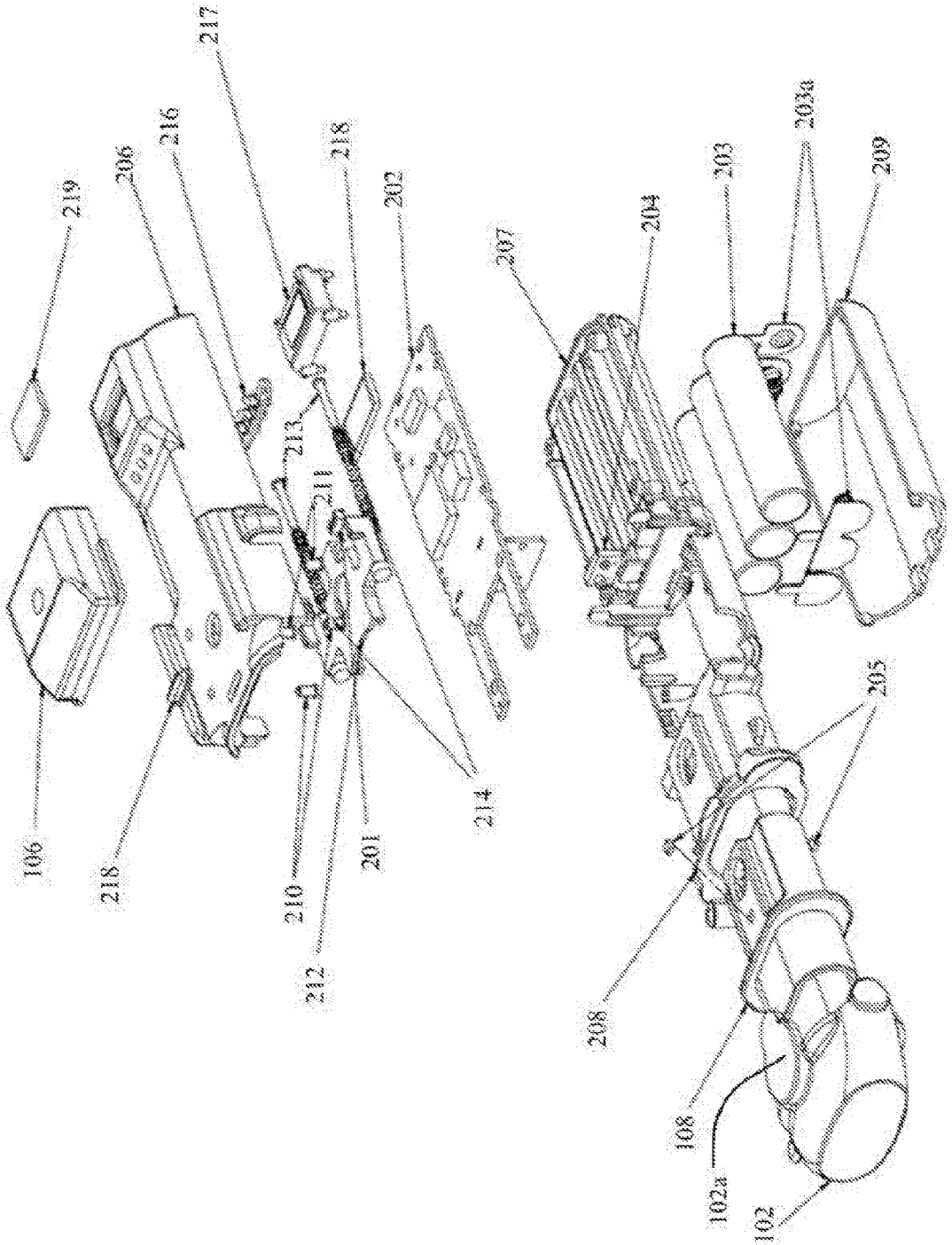

219
206
216
217
218
202
213
211
207
204
203
203a
209
106
218
210
212
201
214
205
208
108
102a
102

FIG. 2

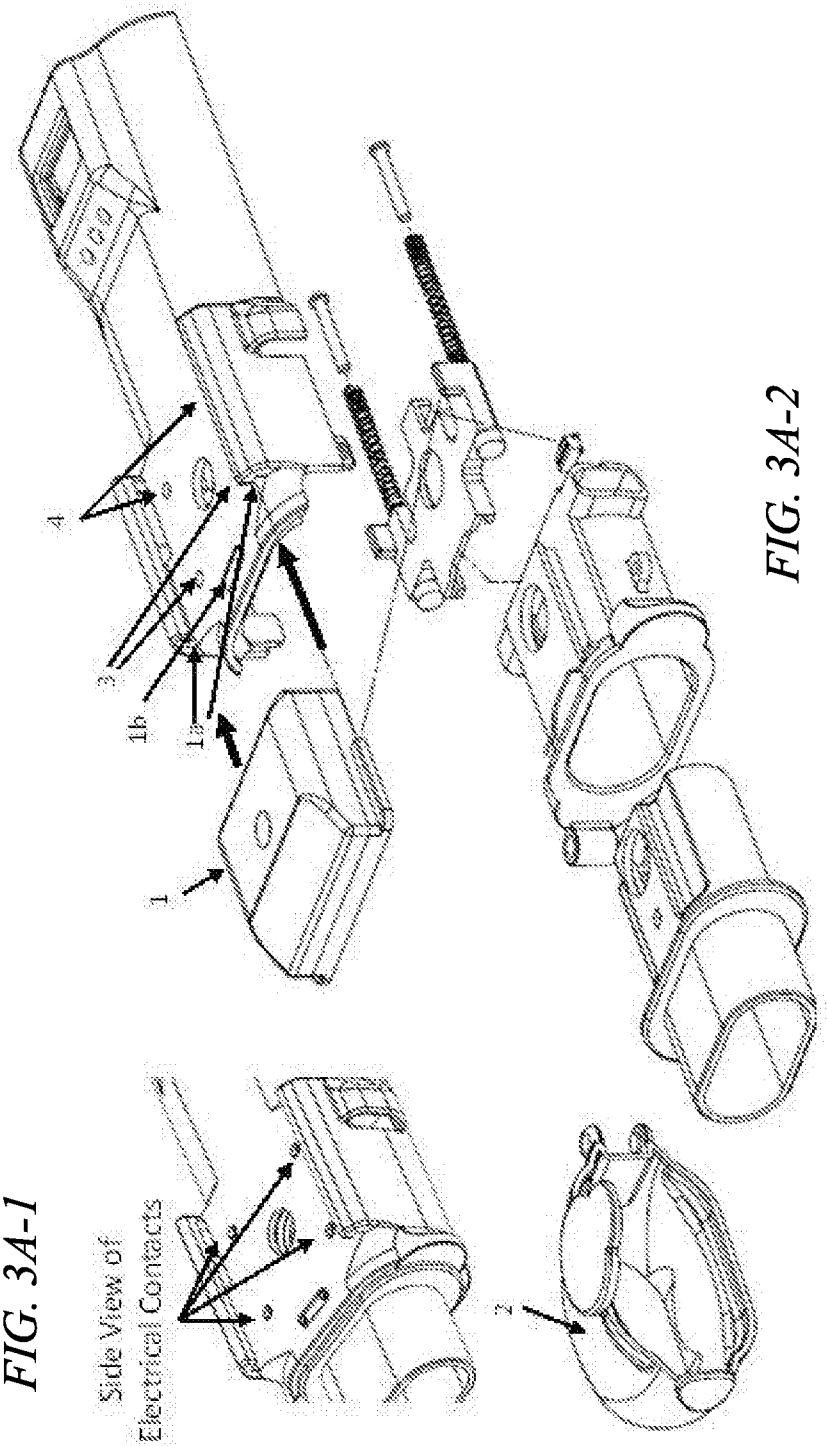


FIG. 3A-1

FIG. 3A-2

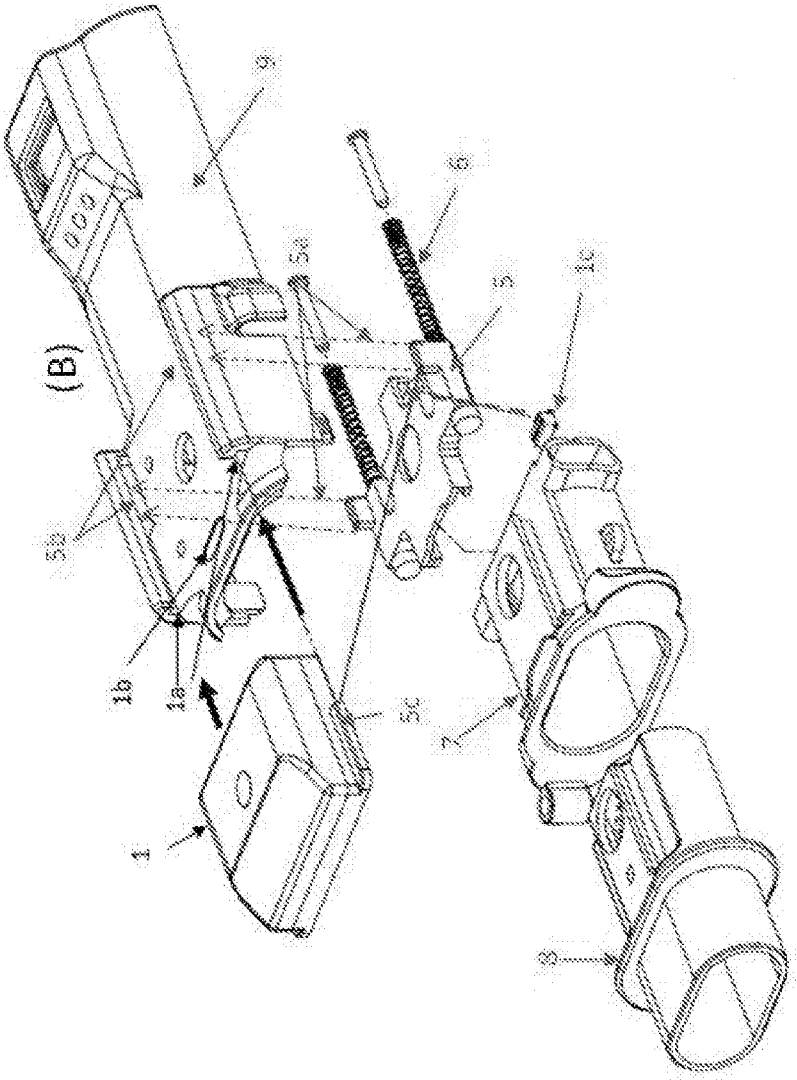


FIG. 3B-2

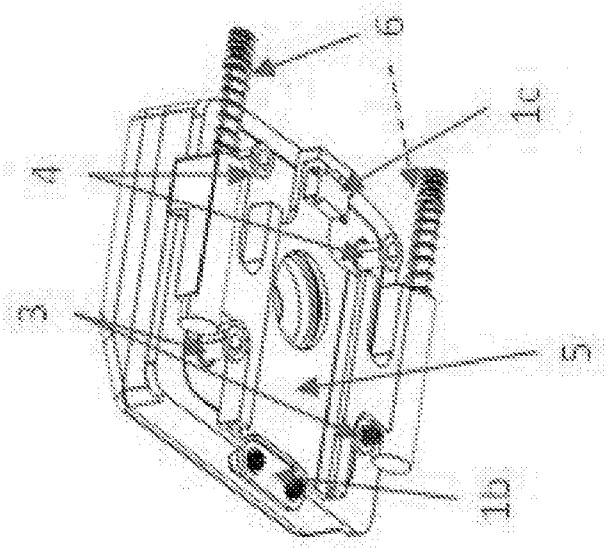
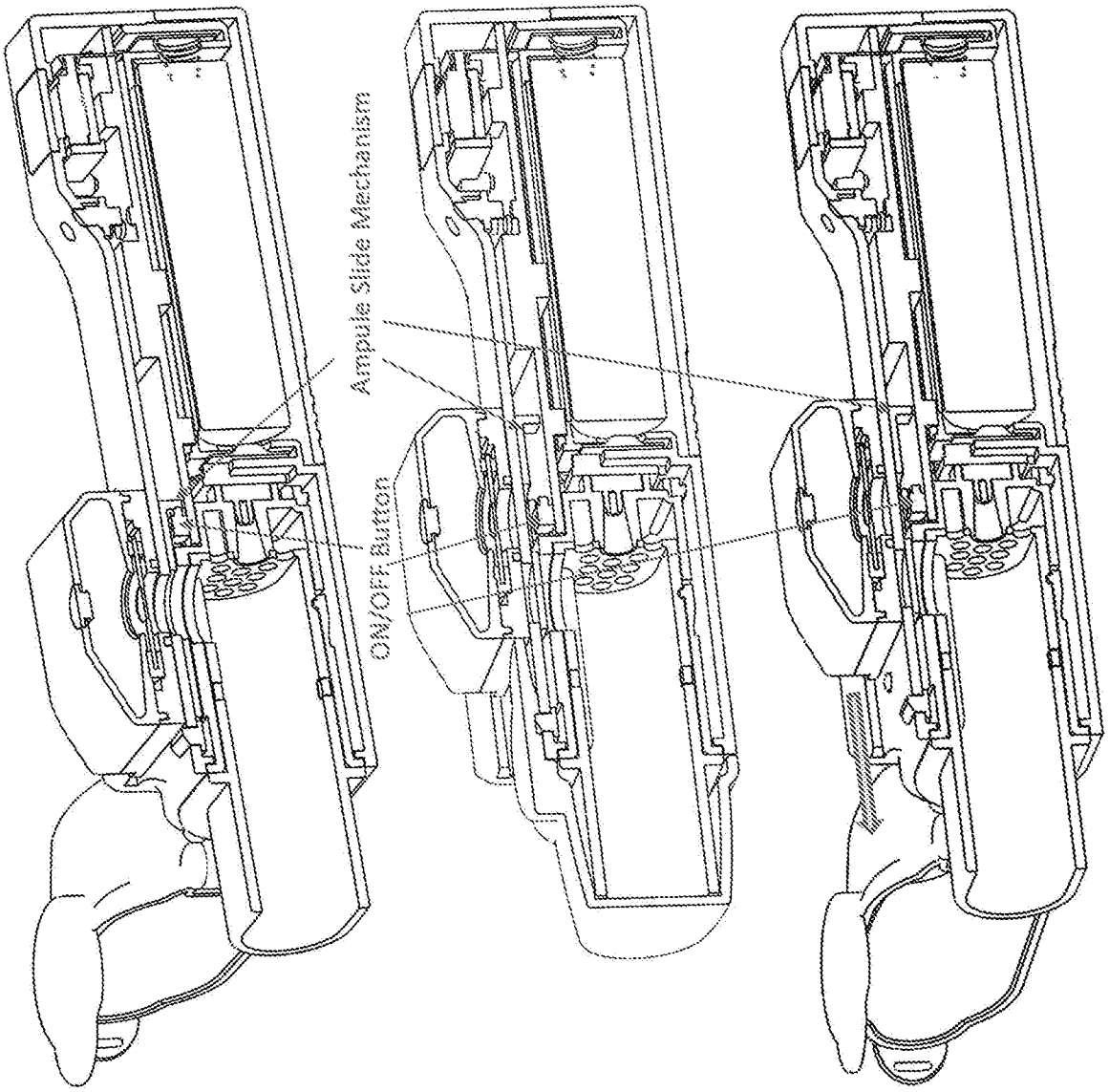


FIG. 3B-1

FIG. 3C-1

FIG. 3C-2

FIG. 3C-3



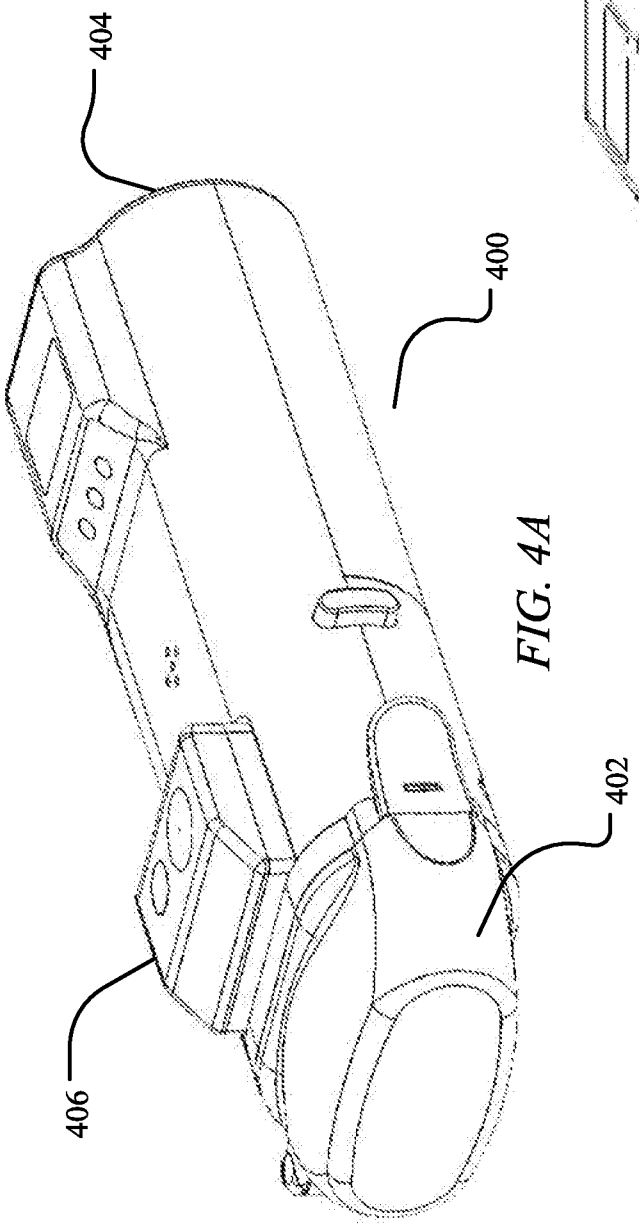


FIG. 4A

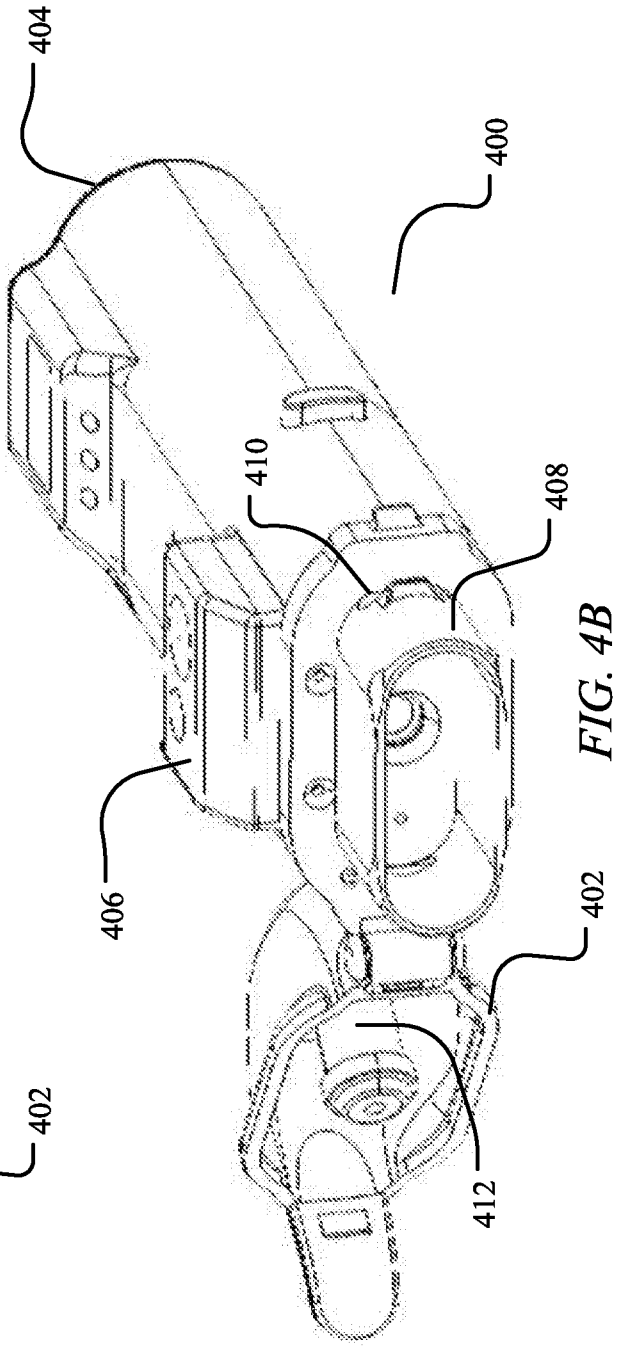


FIG. 4B

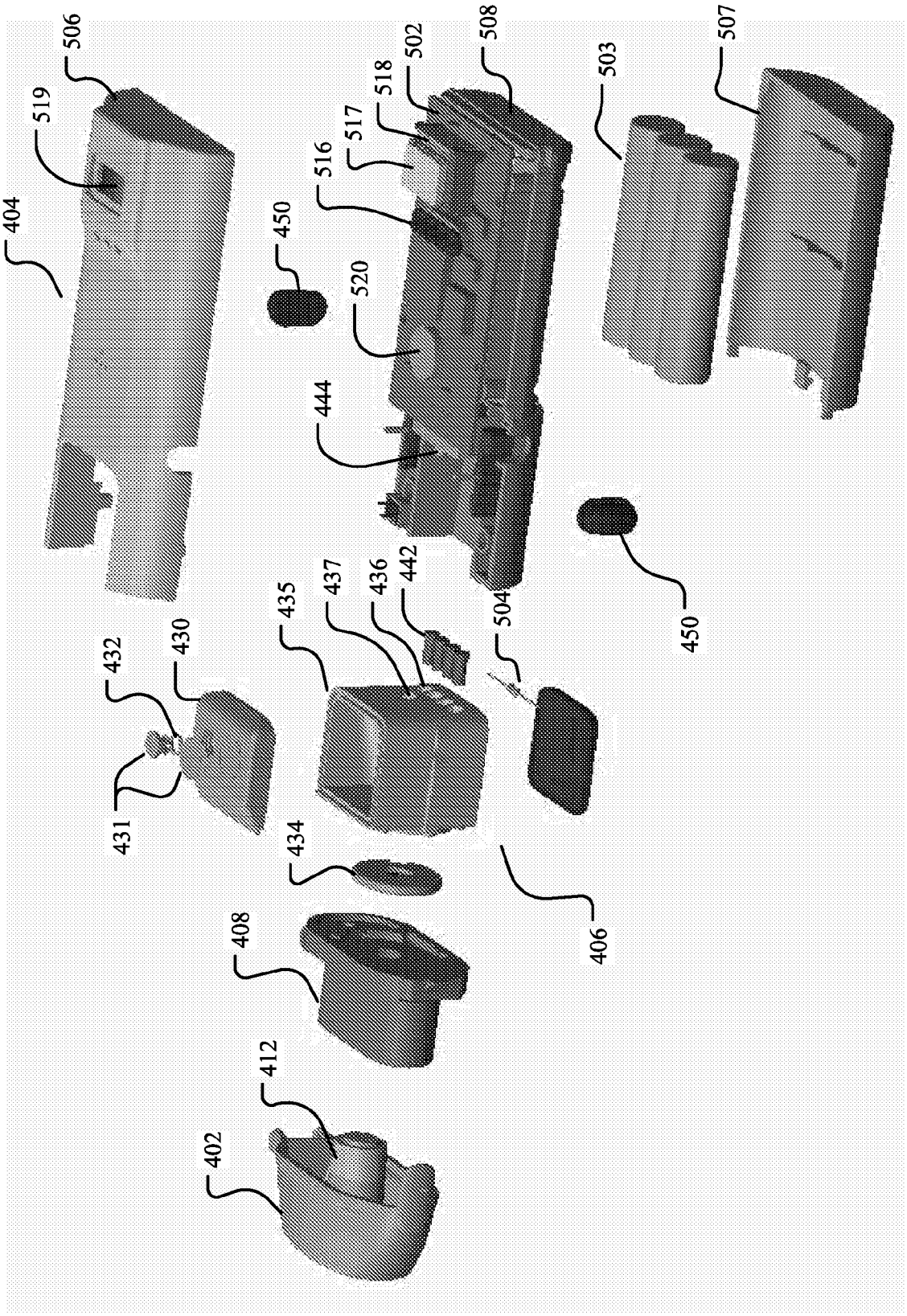

506
519
404
450
516
517
518
502
508
503
507
520
444
437
436
442
435
504
432
430
431
434
408
412
402
406
450

FIG. 5

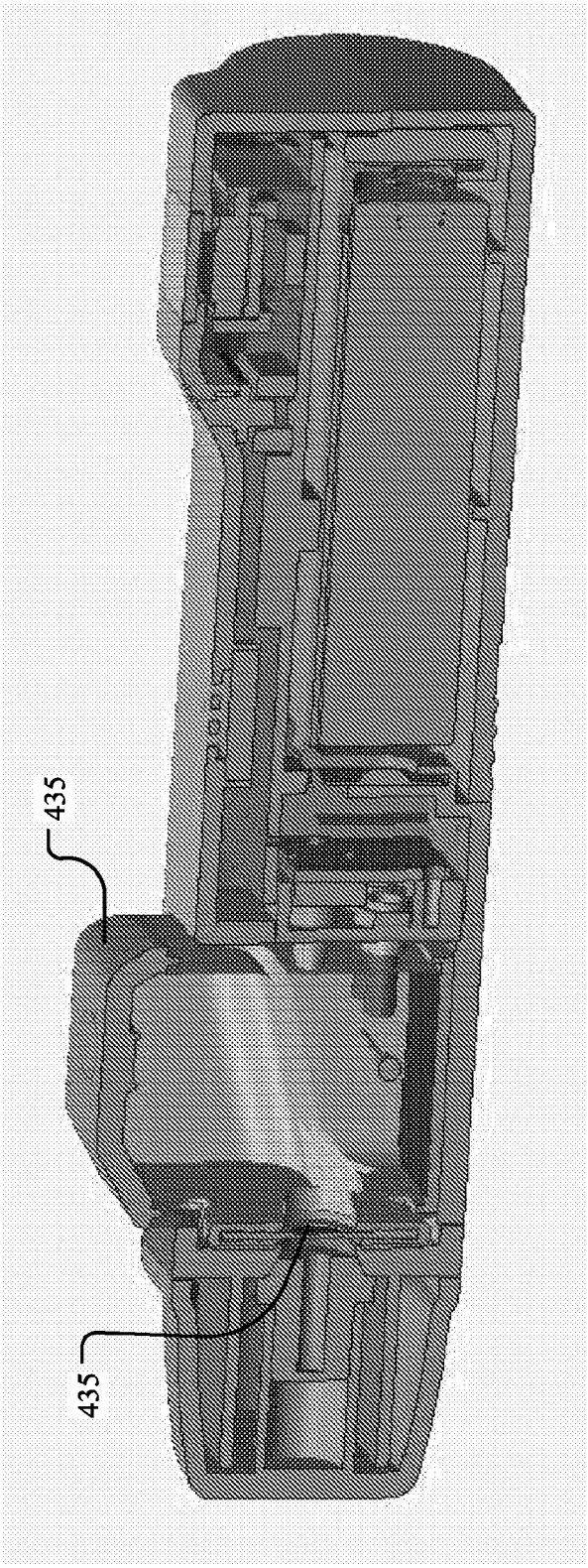


FIG. 6

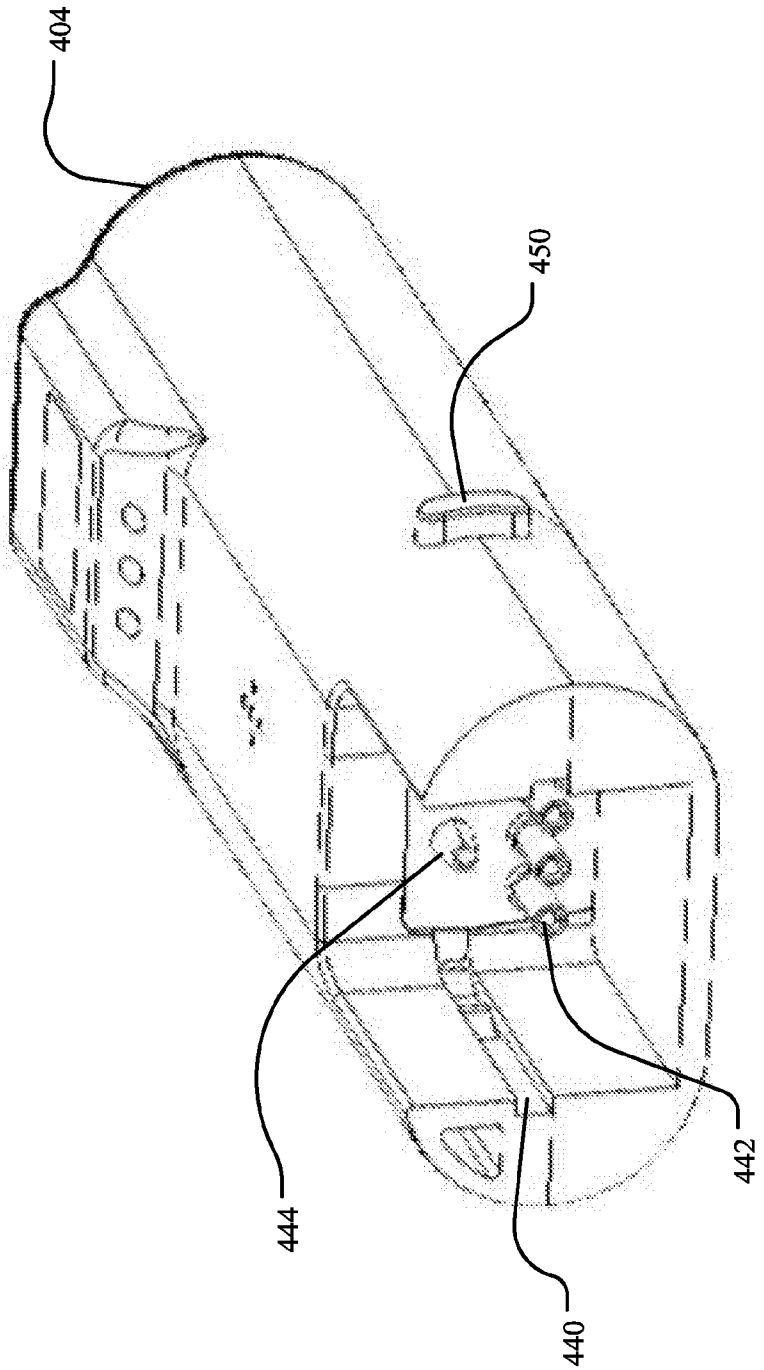


FIG. 7

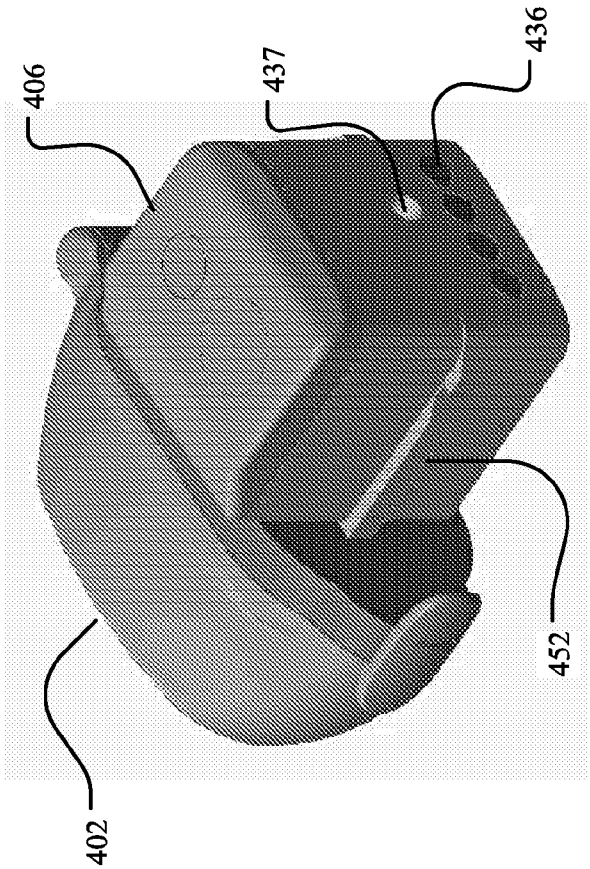


FIG. 8B

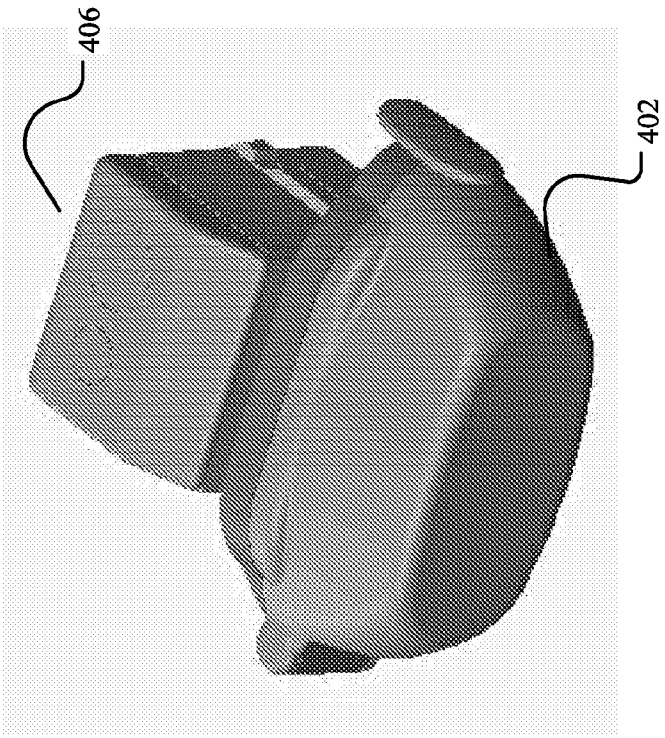


FIG. 8A

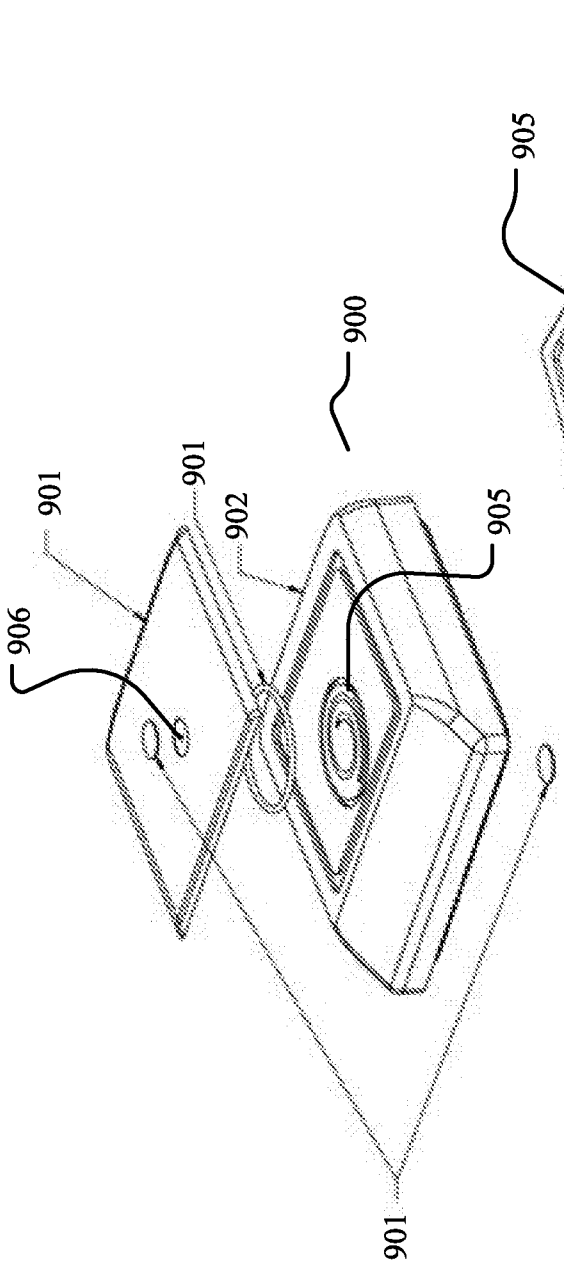


FIG. 9B

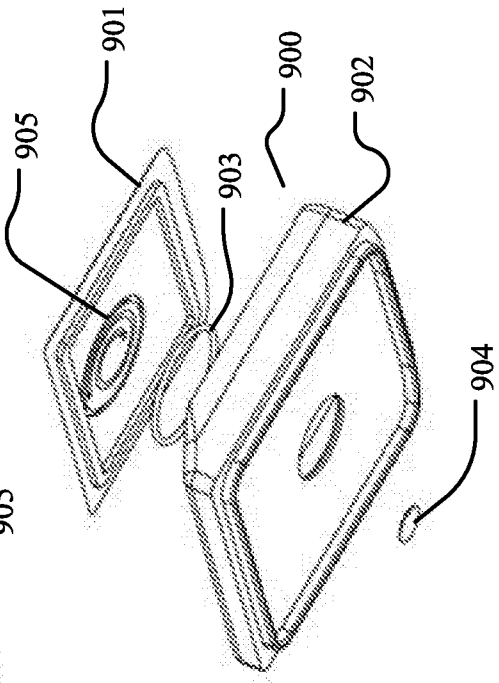


FIG. 9C

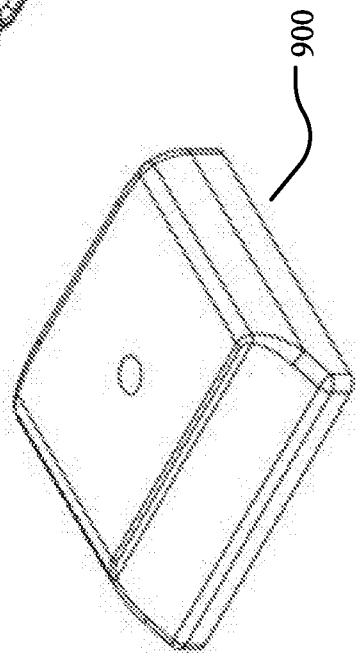


FIG. 9A

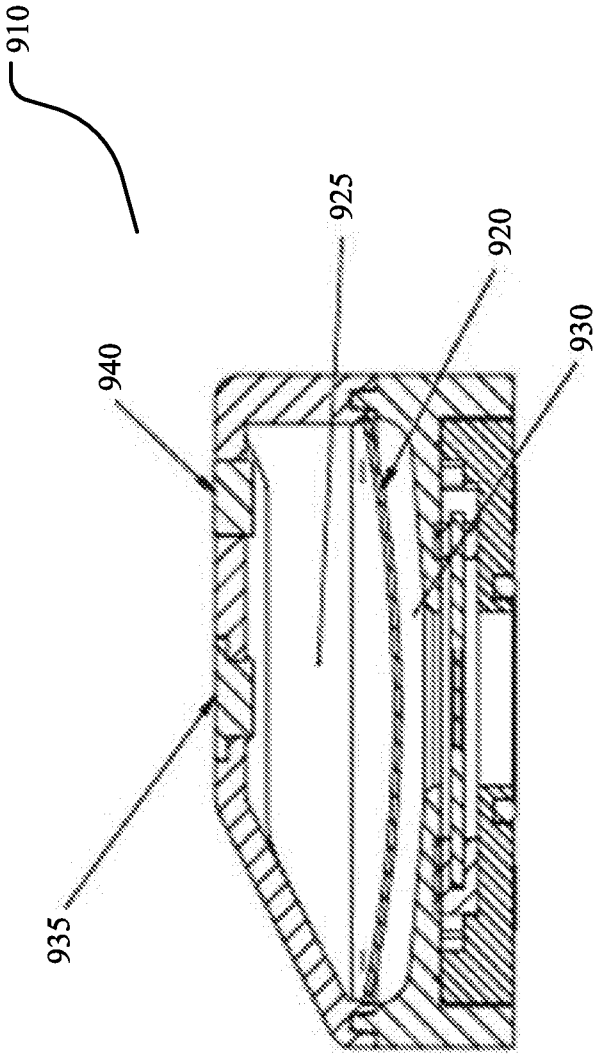


FIG. 9D

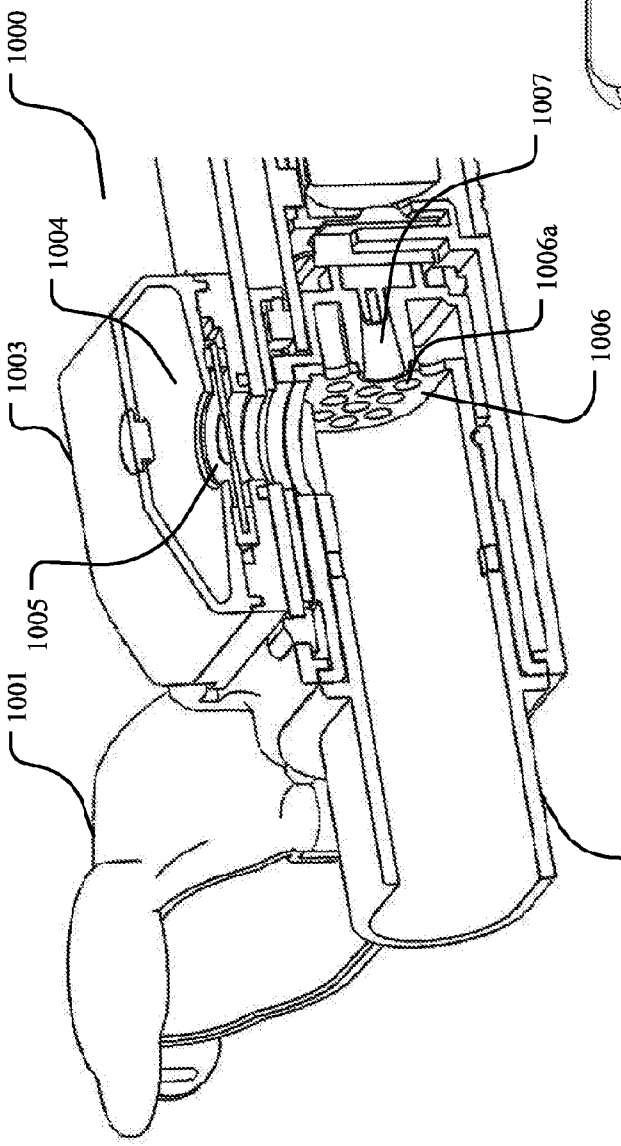


FIG. 10A

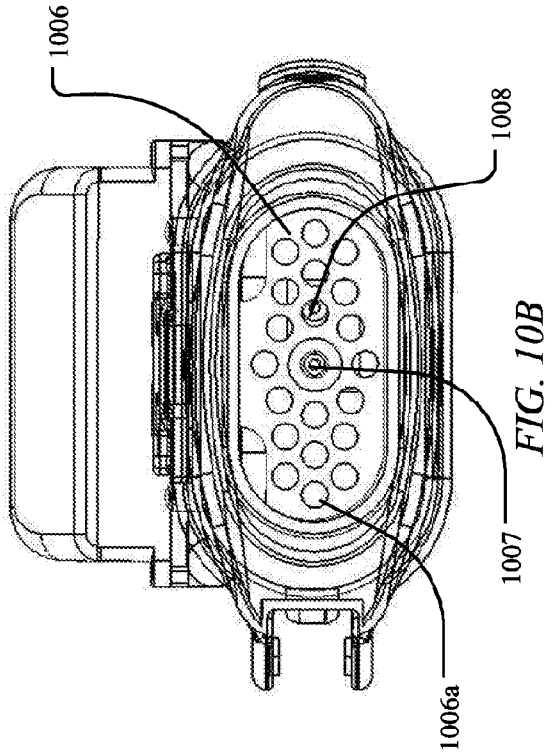


FIG. 10B

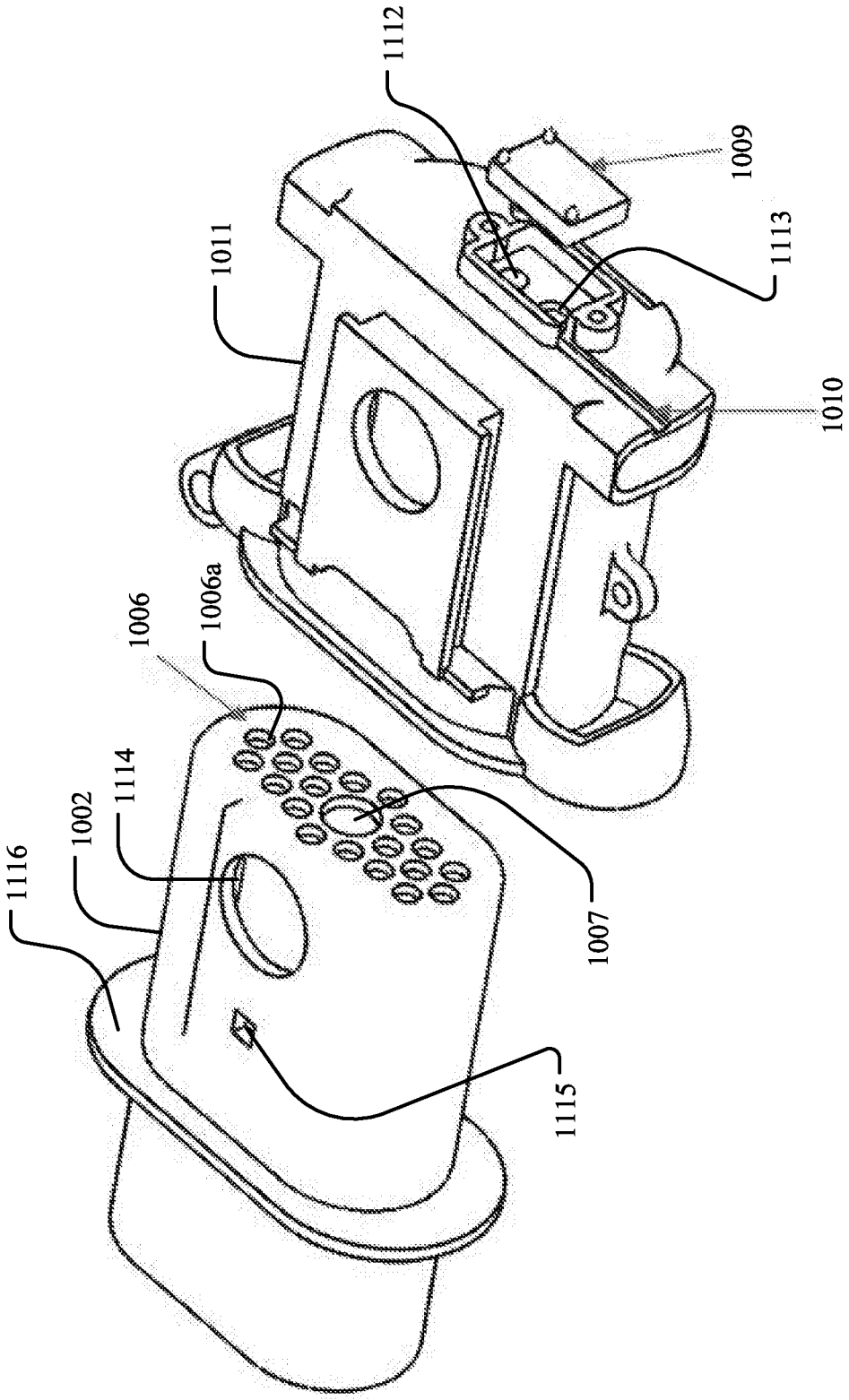


FIG. 10C

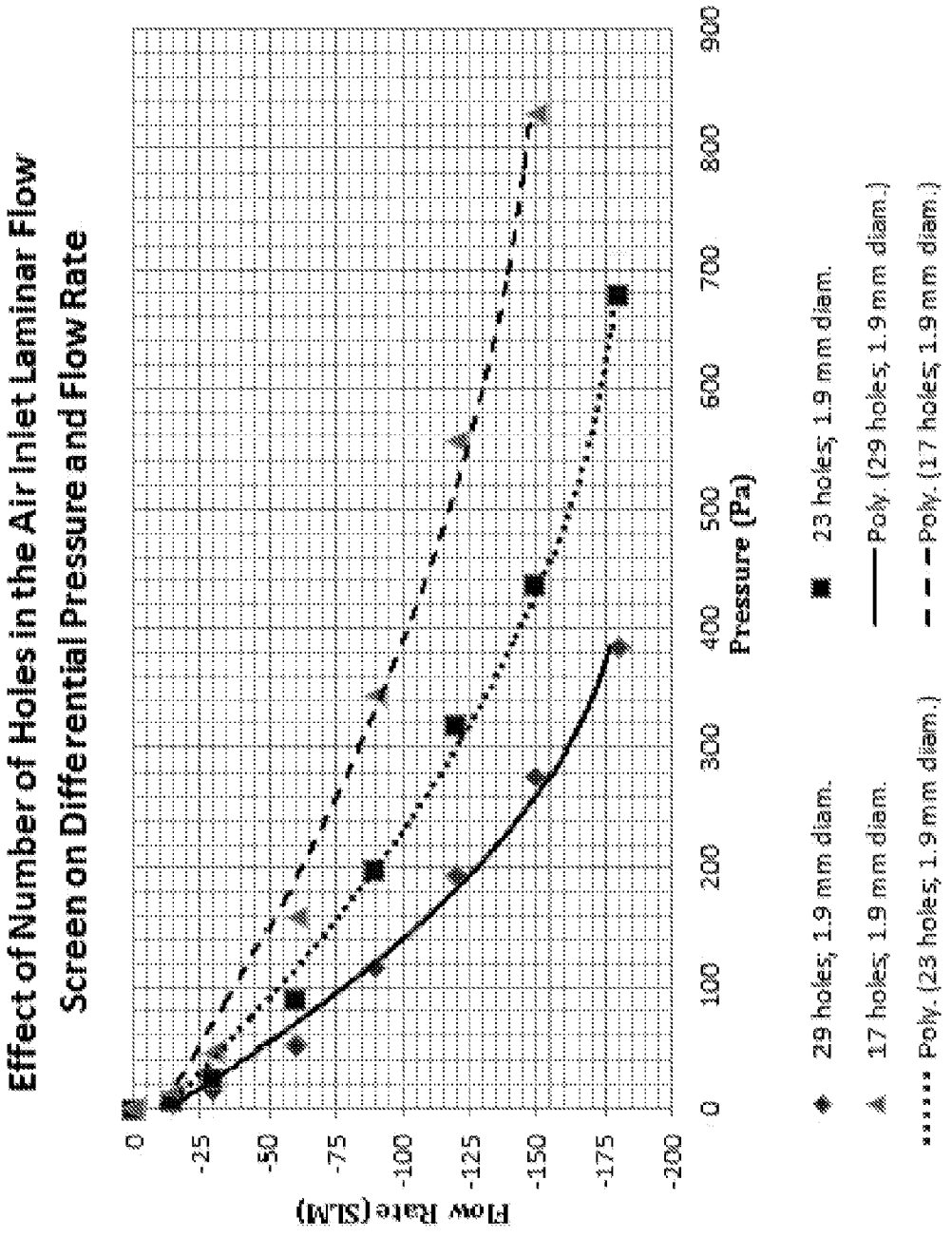

Effect of Number of Holes in the Air Inlet Laminar Flow Screen on Differential Pressure and Flow Rate
Flow Rate (SLM)
0
-25
-50
-75
-100
-125
-150
-175
-200
0
100
200
300
400
500
600
700
800
900
Pressure (Pa)
29 holes; 1.9 mm diam.
23 holes; 1.9 mm diam.
17 holes; 1.9 mm diam.
Poly. (29 holes; 1.9 mm diam.)
Poly. (23 holes; 1.9 mm diam.)
Poly. (17 holes; 1.9 mm diam.)

FIG. 11A

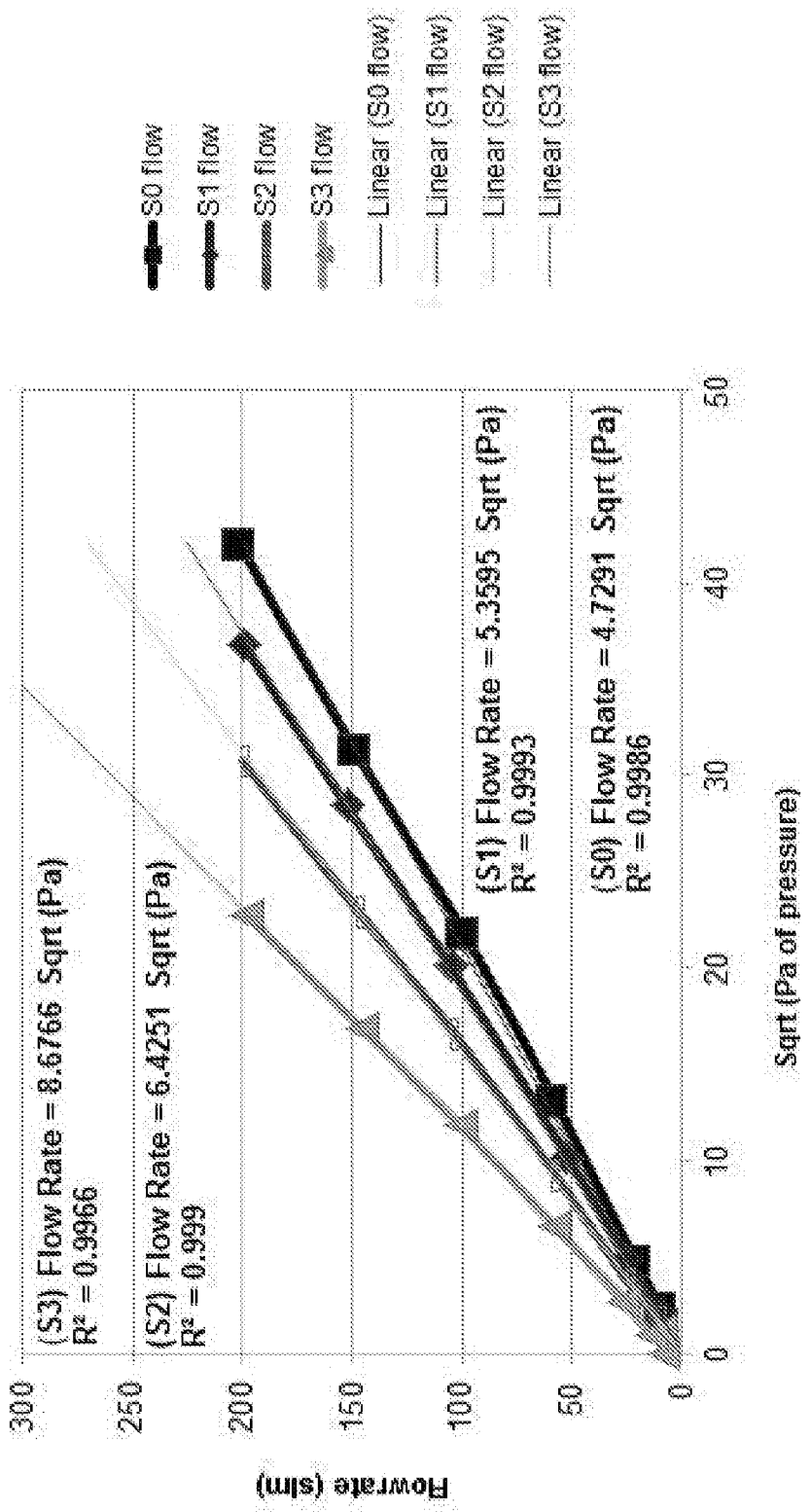

S0 flow
S1 flow
S2 flow
S3 flow
Linear (S0 flow)
Linear (S1 flow)
Linear (S2 flow)
Linear (S3 flow)
(S3) Flow Rate = 8.6766 Sqrt (Pa)
R² = 0.9966
(S2) Flow Rate = 6.4251 Sqrt (Pa)
R² = 0.999
(S1) Flow Rate = 5.3595 Sqrt (Pa)
R² = 0.9993
(S0) Flow Rate = 4.7291 Sqrt (Pa)
R² = 0.9986
Flowrate (slm)
Sqrt (Pa of pressure)
300
250
200
150
100
50
0
0
10
20
30
40
50

FIG. 11B

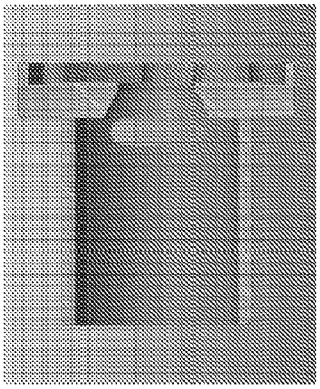


FIG. 12C

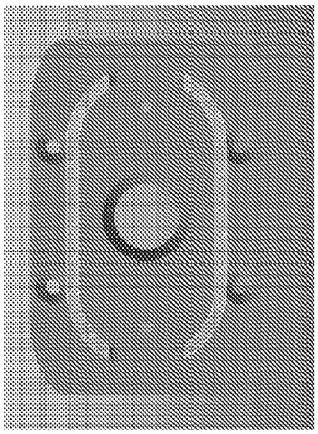


FIG. 12B

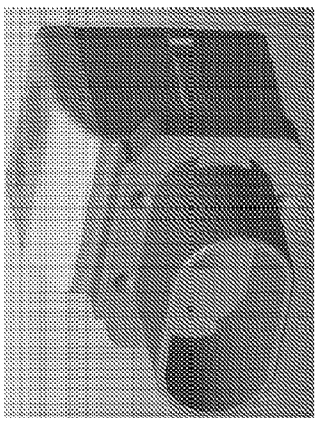


FIG. 12A

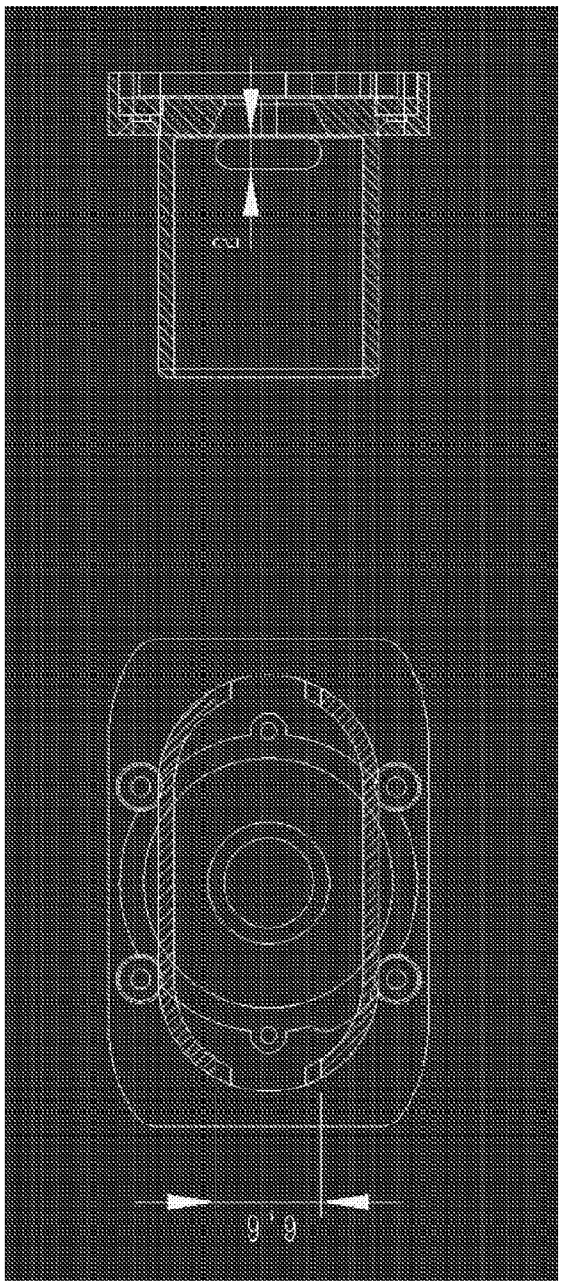


FIG. 12D

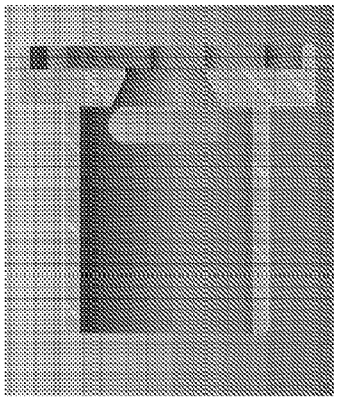


FIG. 13C

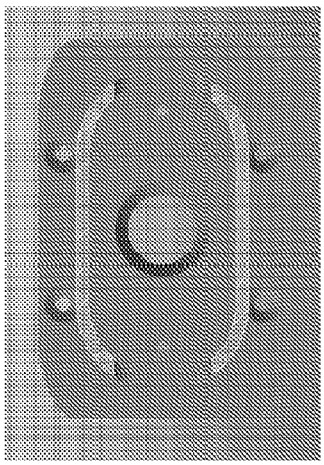


FIG. 13B

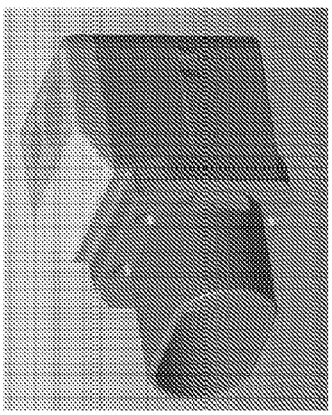


FIG. 13A

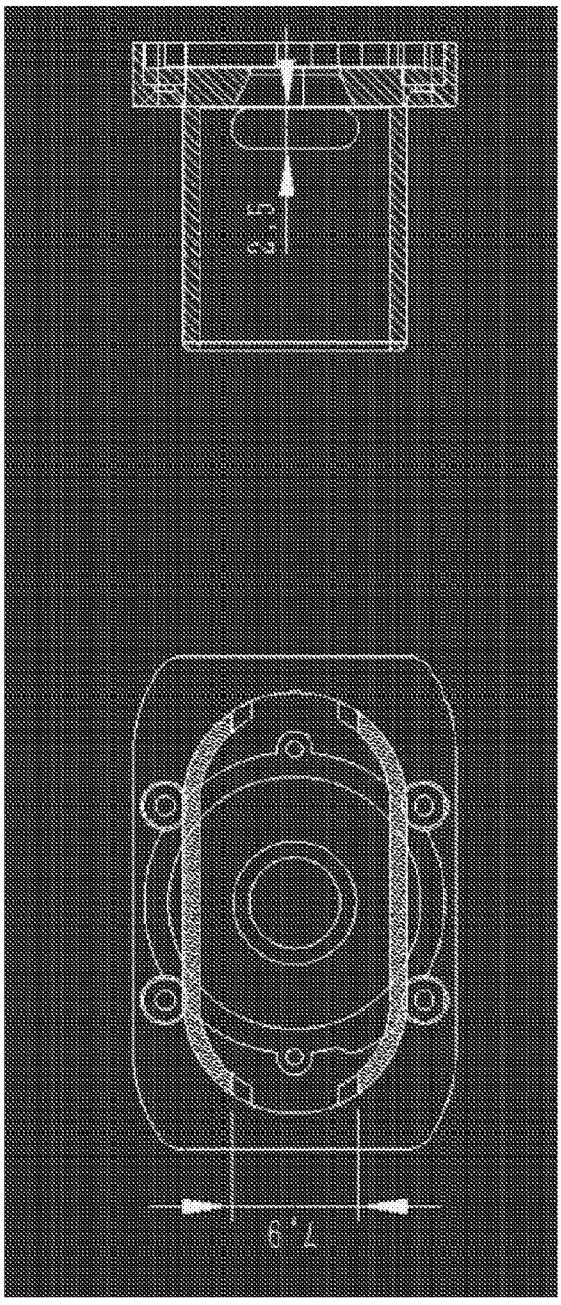


FIG. 13D

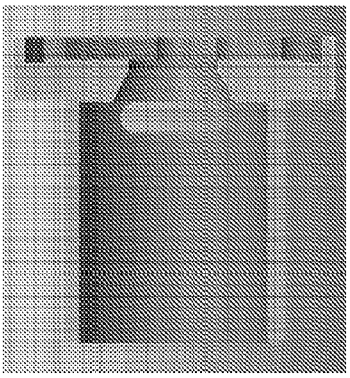


FIG. 14C

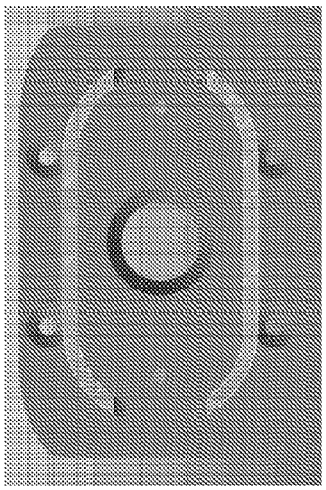


FIG. 14B

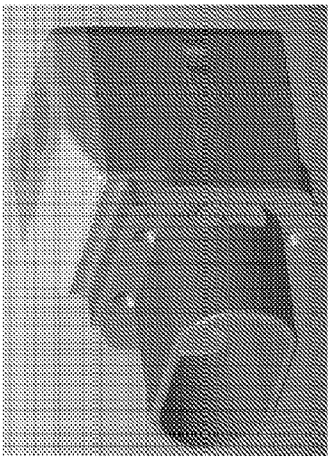


FIG. 14A

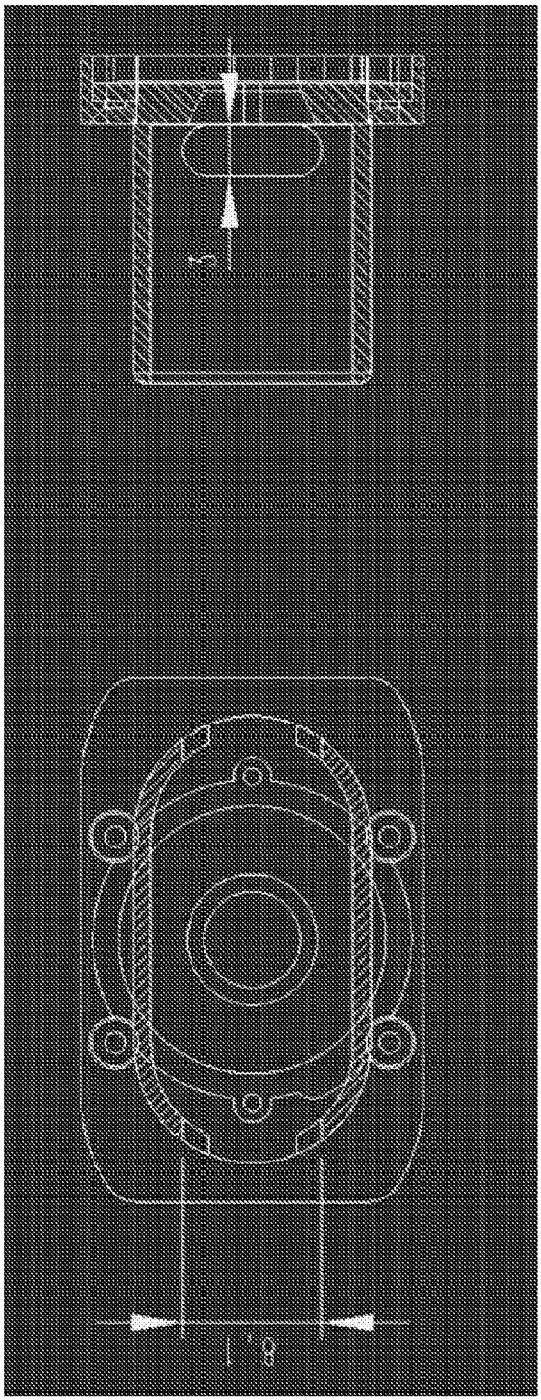


FIG. 14D

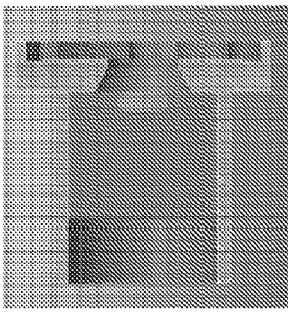


FIG. 15C

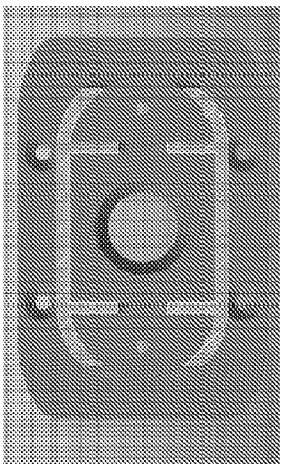


FIG. 15B

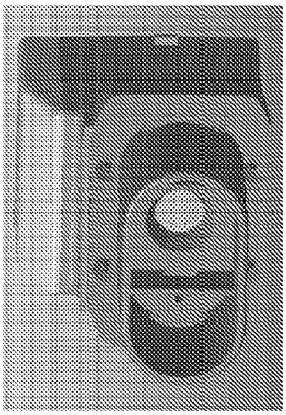


FIG. 15A

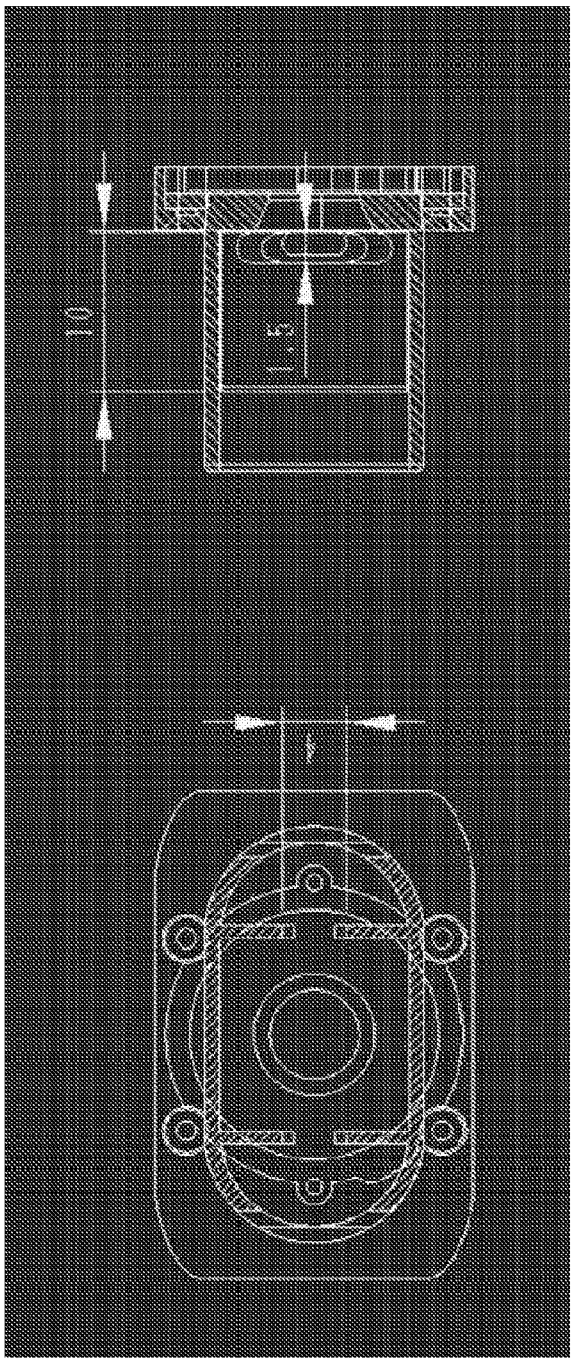


FIG. 15D

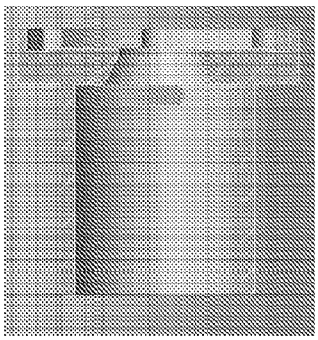


FIG. 16C

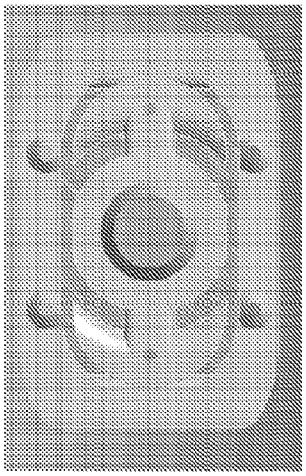


FIG. 16B

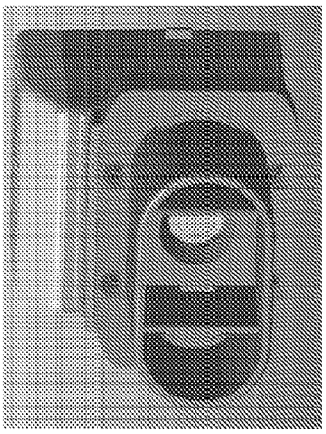


FIG. 16A

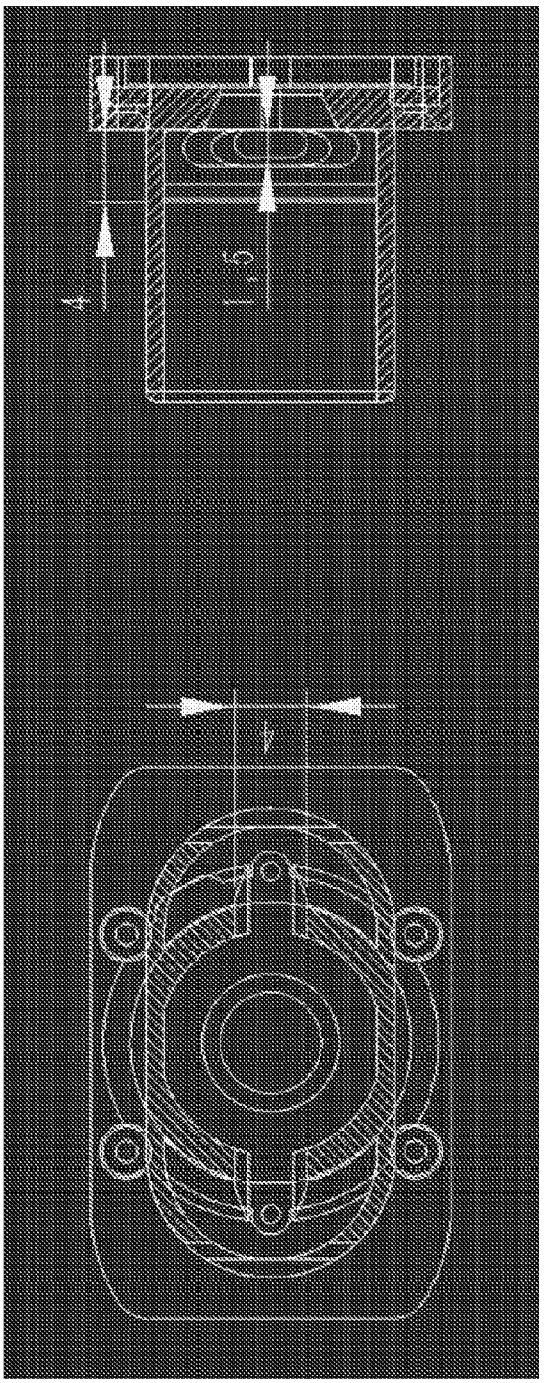


FIG. 16D

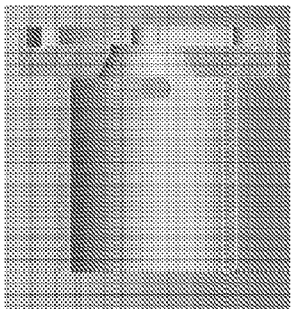


FIG. 17C

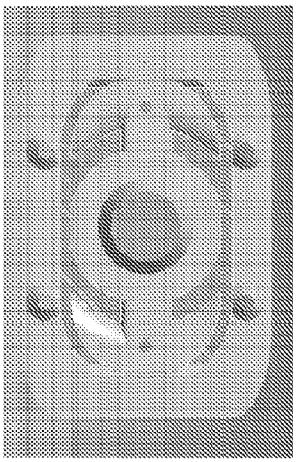


FIG. 17B

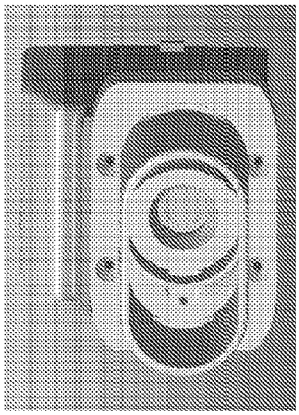


FIG. 17A

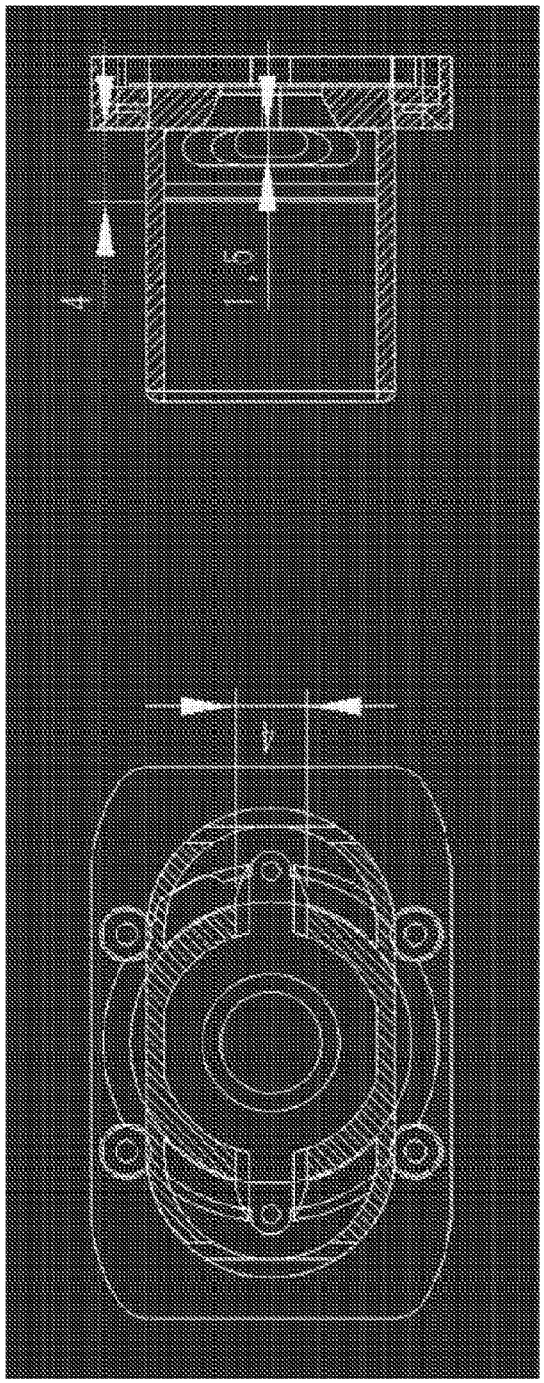


FIG. 17D

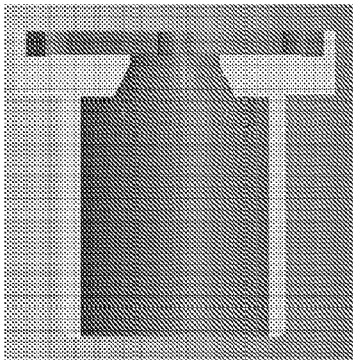


FIG. 18C

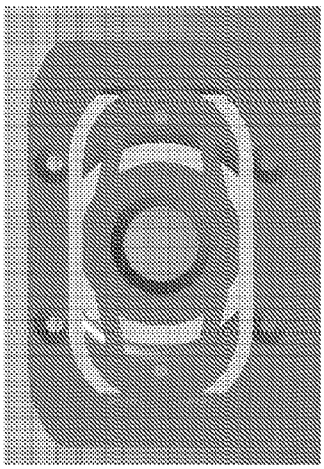


FIG. 18B

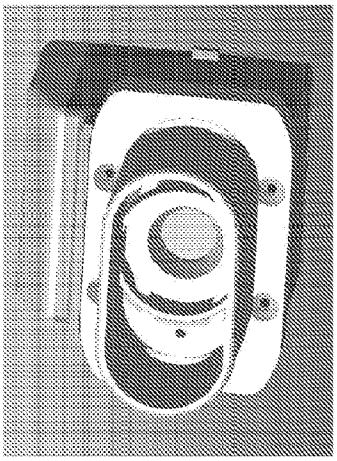


FIG. 18A

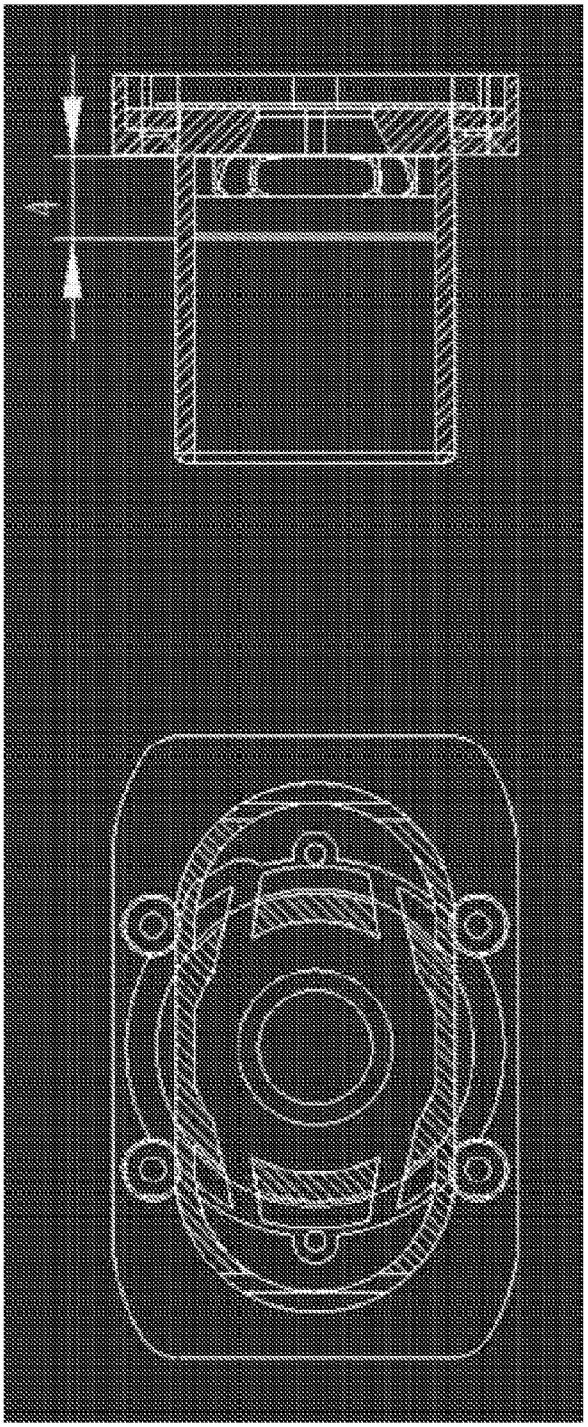


FIG. 18D

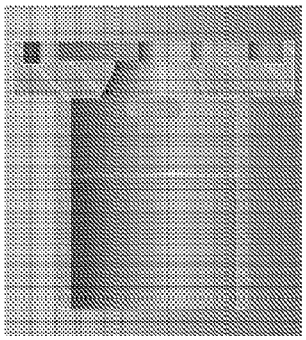


FIG. 19C

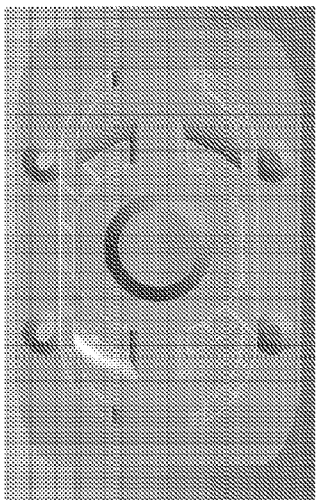


FIG. 19B

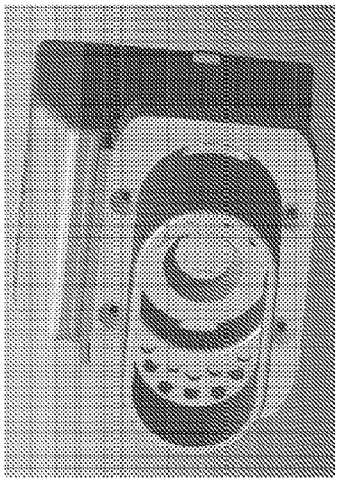


FIG. 19A

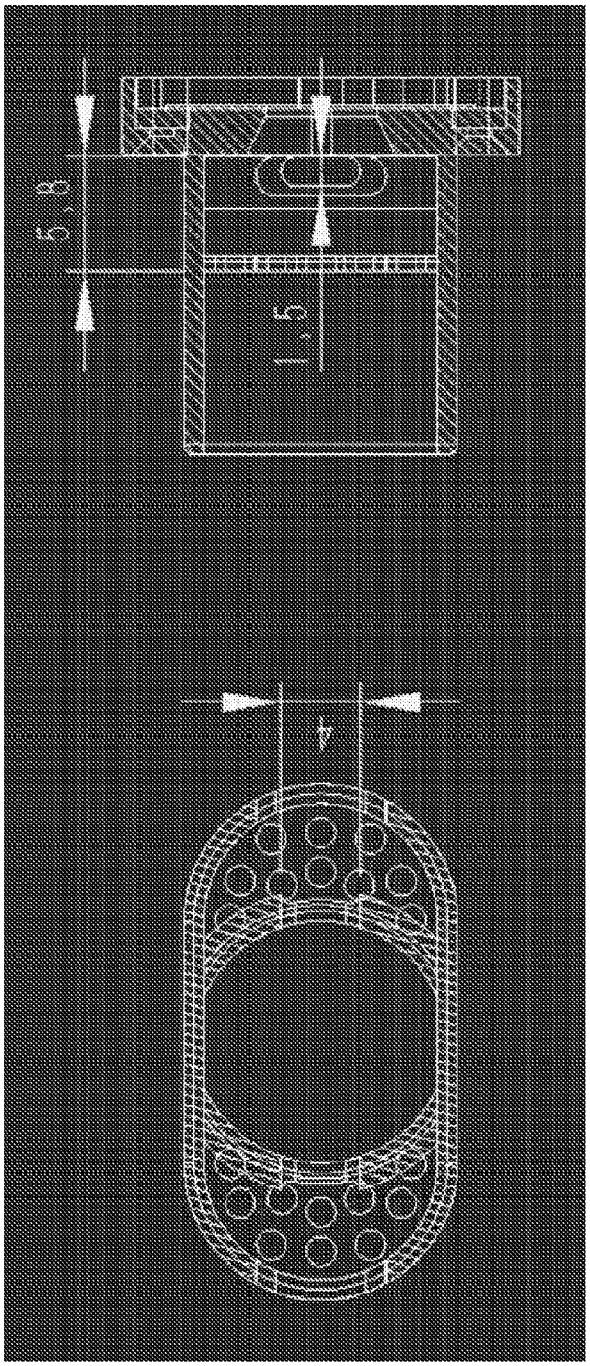


FIG. 19D

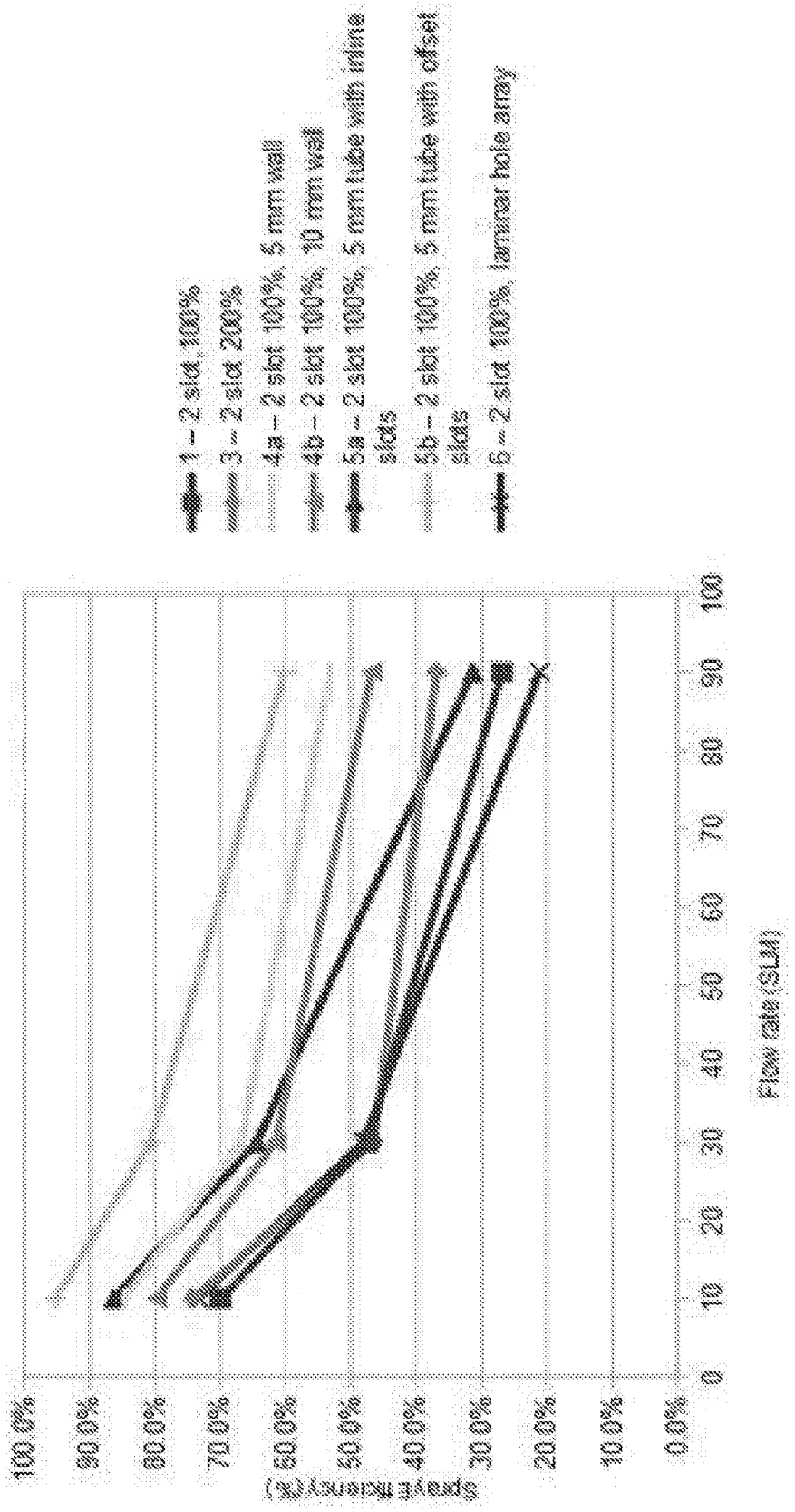

1 – 2 slot, 100%
3 – 2 slot, 200%
4a – 2 slot 100%, 5 mm wall
4b – 2 slot 100%, 10 mm wall
5a – 2 slot 100%, 5 mm tube with inline slots
5b – 2 slot 100%, 5 mm tube with offset slots
6 – 2 slot 100%, laminar hole array
Spray efficiency (%)
100.0%
90.0%
80.0%
70.0%
60.0%
50.0%
40.0%
30.0%
20.0%
10.0%
0.0%
Flow rate (SLM)
0
10
20
30
40
50
60
70
80
90
100

FIG. 20

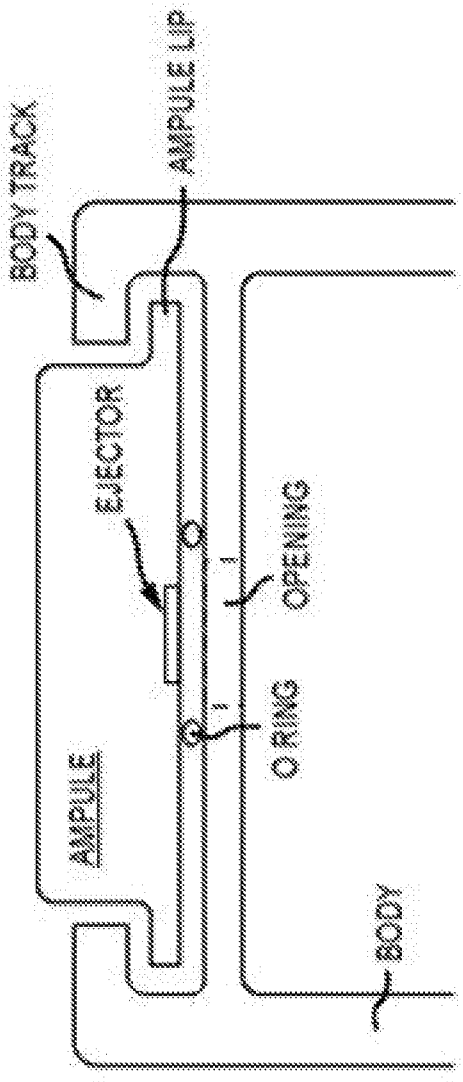

BODY TRACK
AMPULE LIP
EJECTOR
OPENING
O RING
AMPULE
BODY
AMPULE IN TRACK
END VIEW

FIG. 21A

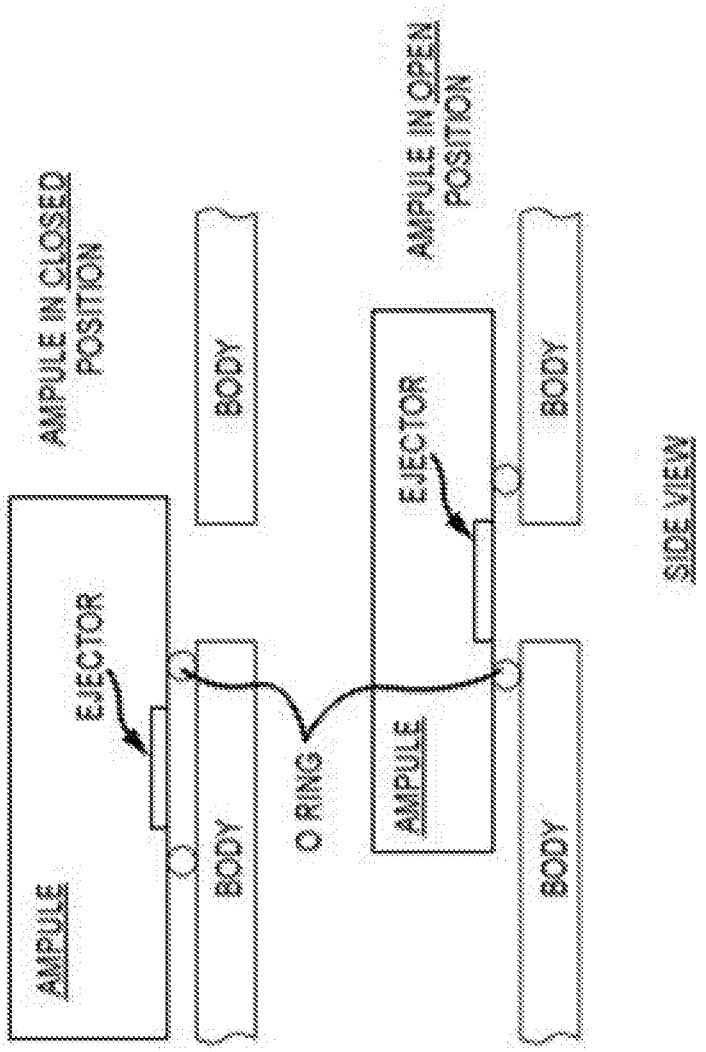

AMPULE IN CLOSED POSITION
AMPULE IN OPEN POSITION
BODY
EJECTOR
O RING
AMPULE
SIDE VIEW

FIG. 21B

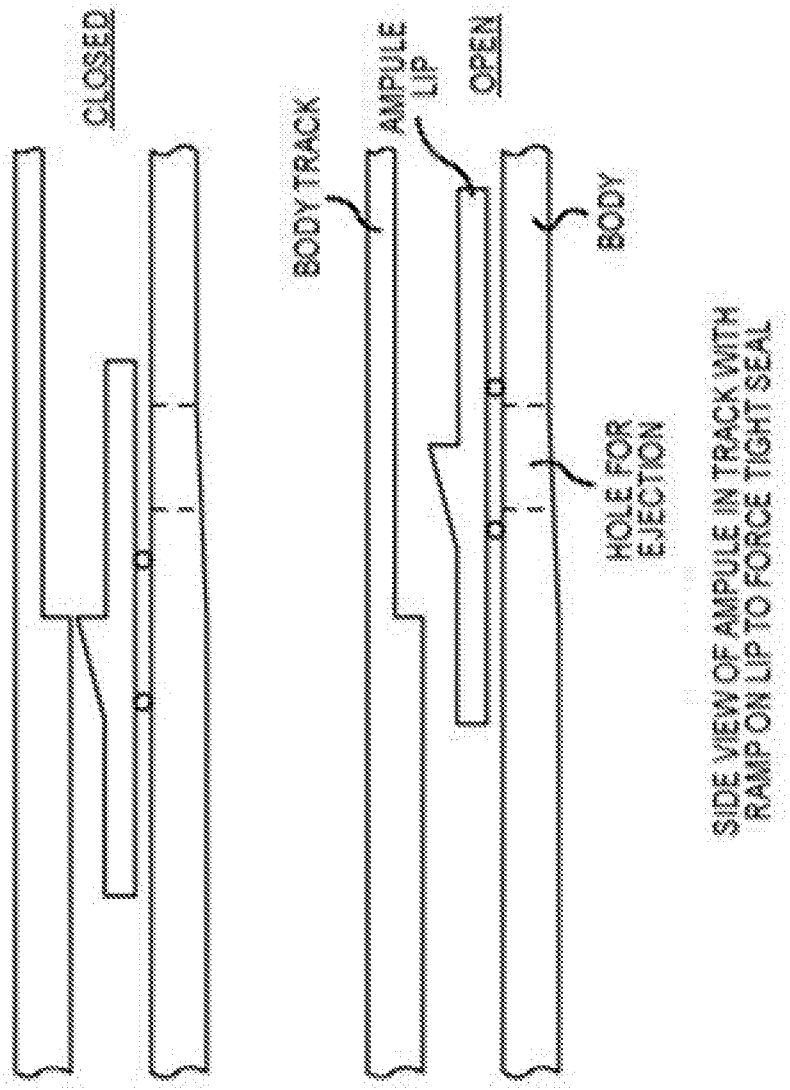

CLOSED
BODY TRACK
AMPULE LIP
OPEN
BODY
HOLE FOR EJECTION
SIDE VIEW OF AMPULE IN TRACK WITH RAMP ON LIP TO FORCE TIGHT SEAL

FIG. 21C

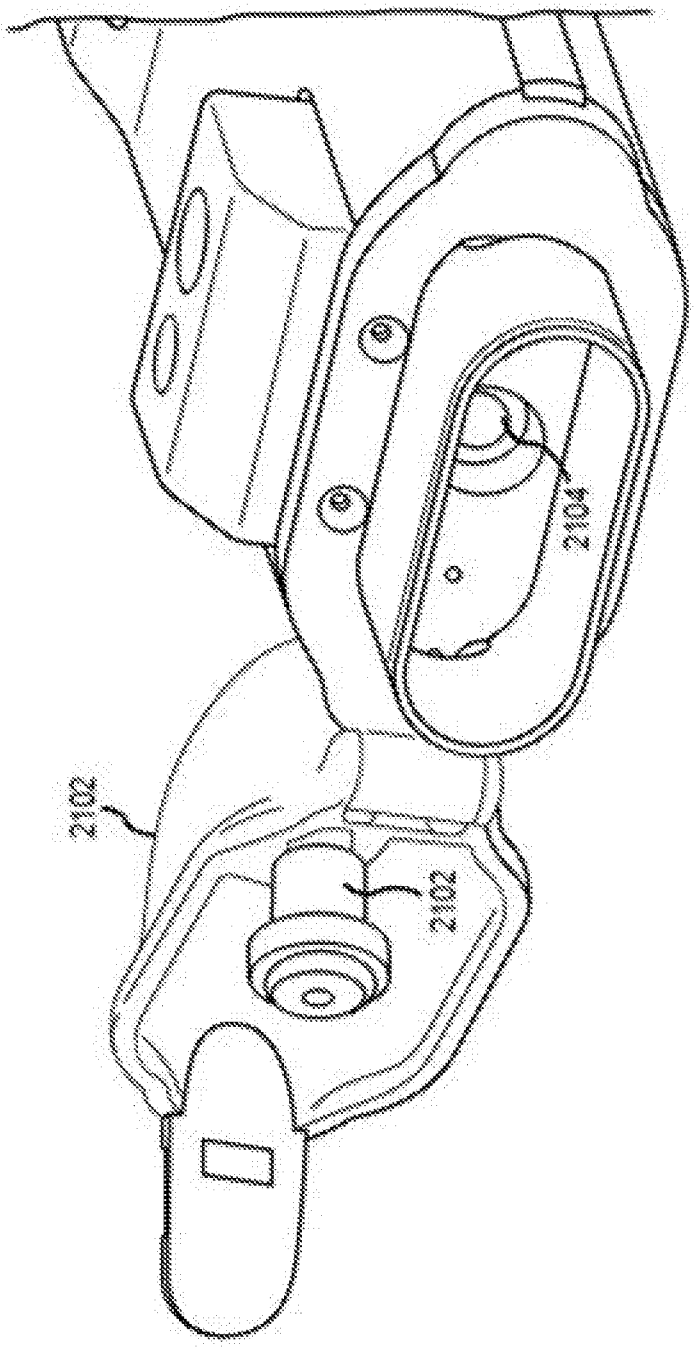


FIG. 21D

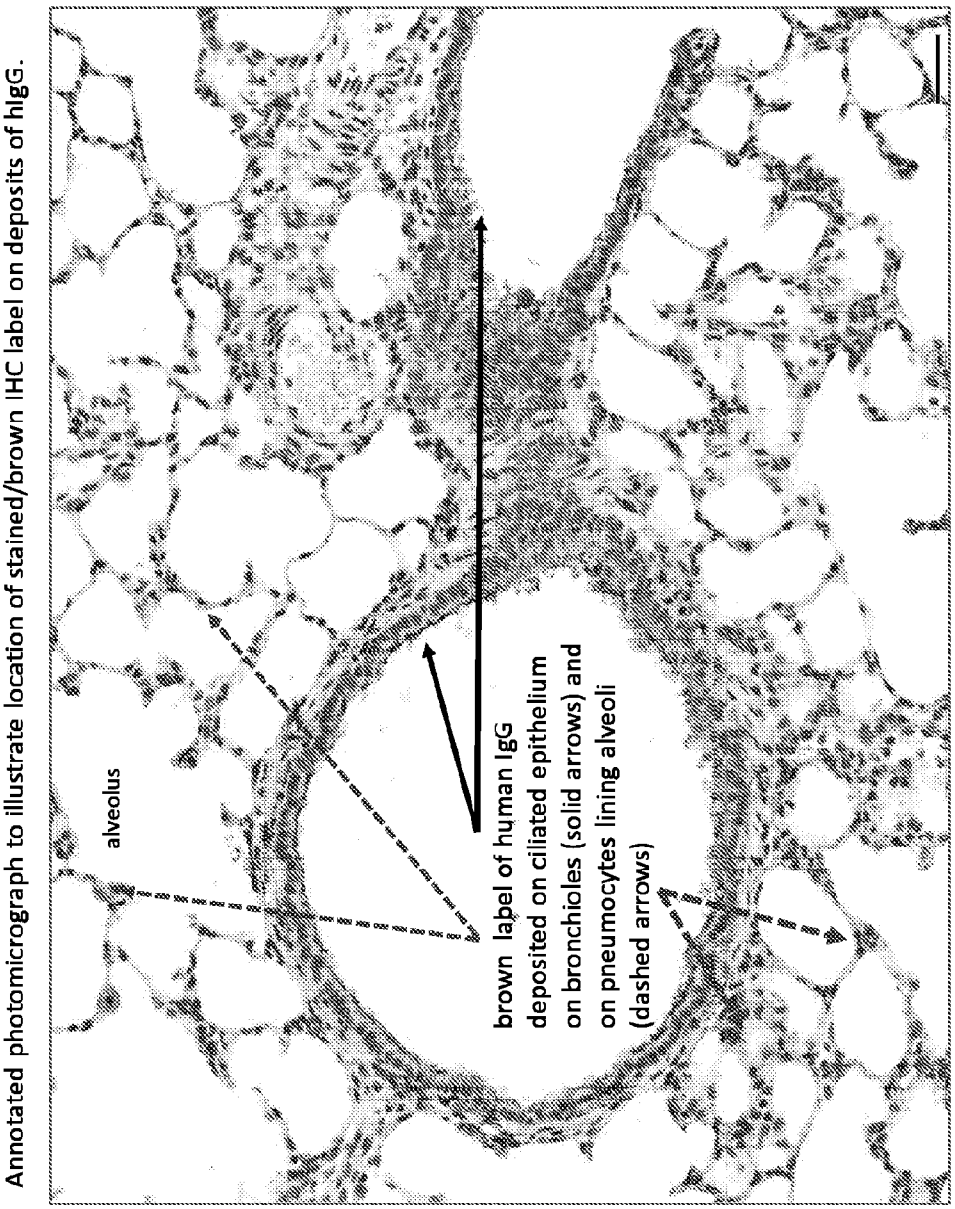

Annotated photomicrograph to illustrate location of stained/brown IHC label on deposits of hIgG.
alveolus
brown label of human IgG deposited on ciliated epithelium on bronchioles (solid arrows) and on pneumocytes lining alveoli (dashed arrows)
Section probed with anti-human IgG and visualized with DAB chromogen; photographed with 20x magnification; lung from Group 2: rat 2.1

FIG. 22A

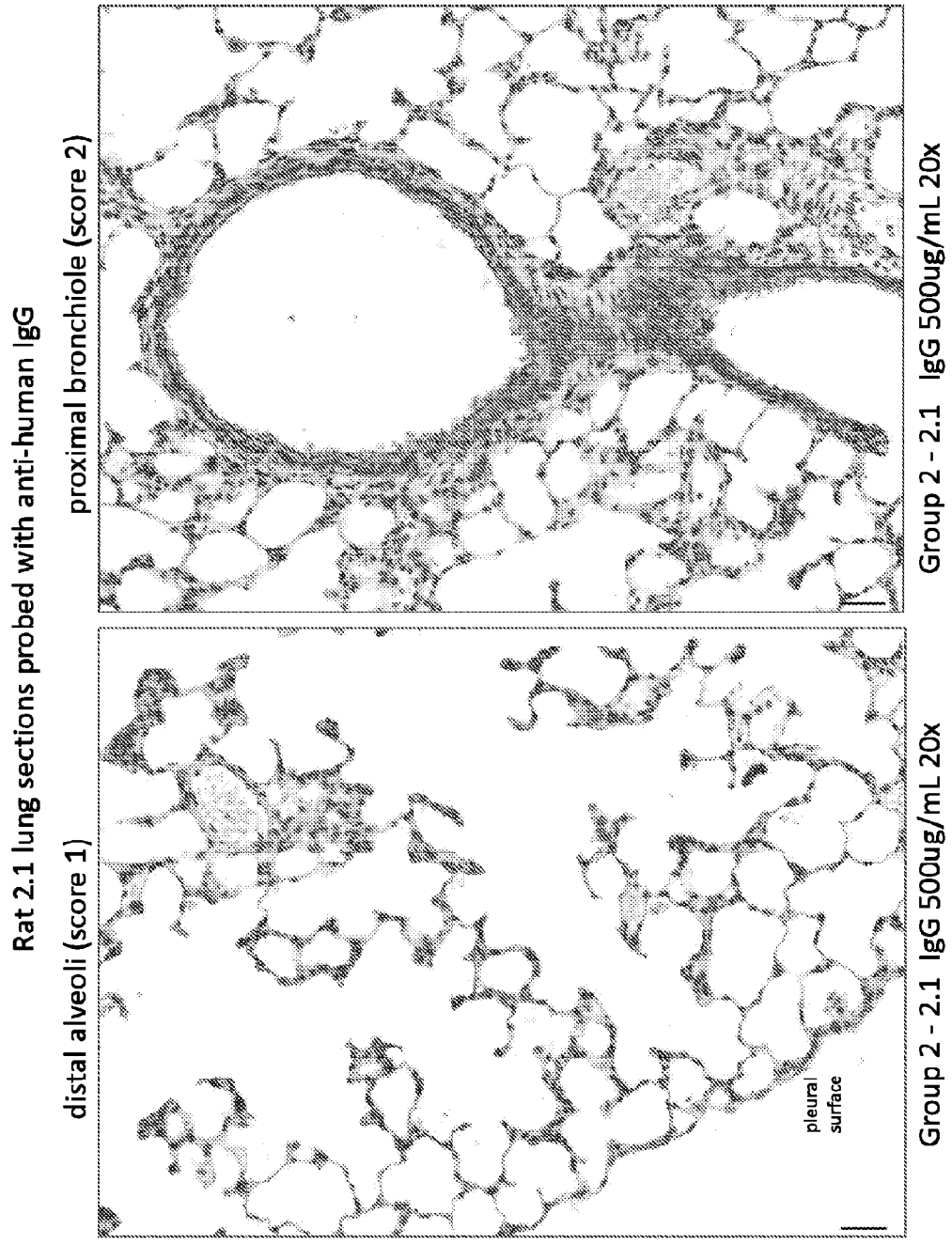


FIG. 22B

FIG. 22C

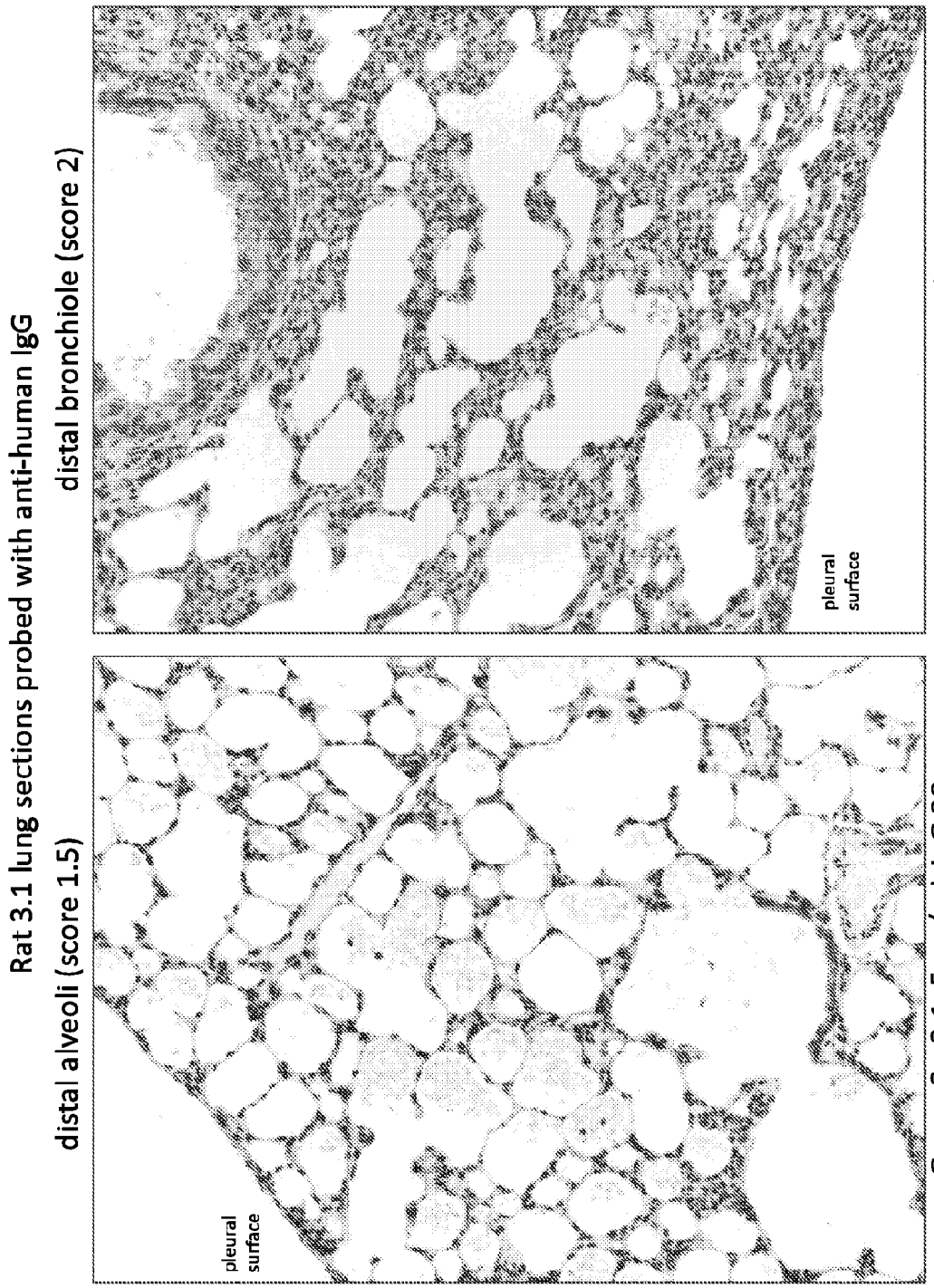


FIG. 22D

FIG. 22E

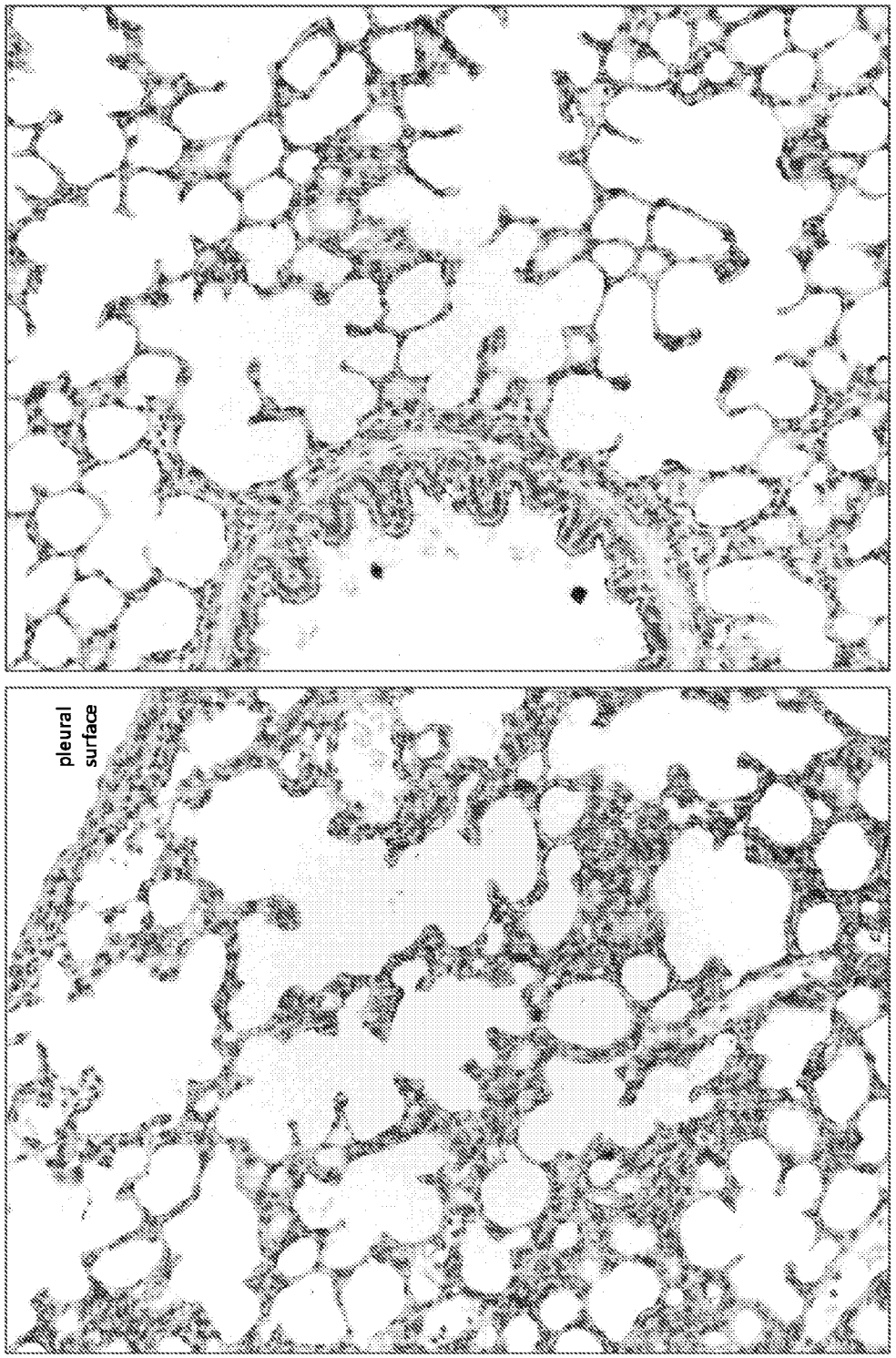


FIG. 22F

FIG. 22G

FIG. 1A