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(54) Title: INSUFFLATION APPARATUS AND METHODS

(57) Abstract: An insufflation apparatus and methods for using same are disclosed. The apparatus is equipped with an interactive system for administering reproducible intratracheal aerosols in a consistent automated manner. The insufflation system is useful, in particular for use with experimental animals, including mice and rats and also for treating small animals via the pulmonary route in veterinary medicinal practice.

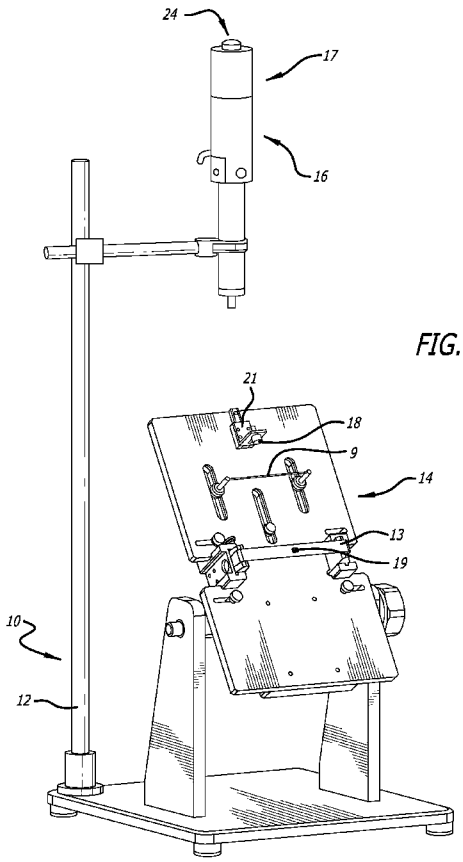

FIG. 1

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INSUFFLATION APPARATUS AND METHODS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. provisional patent application number 61/862,484, filed August 5, 2013, the entire disclosure of which is incorporated herein by reference.

TECHNICAL FIELD

[0002] The present disclosure relates to a drug delivery system, including an insufflation apparatus and methods for delivering a consistent powder discharge to an animal's lungs during inhalation cycles. In particular, the apparatus is configured with an automated computerized system which can be used to deliver drugs by insufflation, for example, to experimental animals for local and/or systemic drug administration studies. The apparatus achieves drug delivery with consistency and reproducibly.

[0003] All references cited in this specification, and their references, are incorporated by reference herein in their entirety where appropriate for teachings of additional or alternative details, features, and/or technical background.

BACKGROUND

[0004] The pulmonary route of administration is useful for delivering medicines into the lungs for treatment of local conditions or to achieve systemic absorption. For local treatments, the medicine can be delivered directly to the site of need where the compound can exert effect. Most current drugs delivered to the lungs are designed to have an effect on the tissue of the lungs. Examples of drugs for lung delivery include, vasodilators, surfactants, chemotherapeutic agents, or vaccines for flu, or other respiratory illnesses for the treatment of diseases, including, asthma, COPD, cystic fibrosis, and pulmonary infections. Pulmonary administration enables rapid treatment of these chronic and acute conditions. Drug formulations for treating pulmonary diseases such as asthma are available by several methods, including, using nebulizers such as treatment with PULMOZYME®, using metered-dose inhalers such as SYMBICORT®, and dry powder inhalers such as ADVAIR DISKUS®, PULMICORT FLEXHALER®.

Other types of treatments, including biologics such as nucleotides drugs in genetic therapy have been delivered to the lungs, for example, for gene therapy of cystic fibrosis, where retroviral vectors expressing an effective adenosine deaminase are administered to the lungs.

[0005] Currently, formulations for treating systemic disease using biologic products are available primarily through injectable compositions. Dry powder compositions for pulmonary inhalation and systemic delivery of insulin have been used, including EXUBERA®, and AFREZZA®.

[0006] In cases where systemic absorption is desired, the large surface area of the lung, its thin wall structure, and its local proximity to the systemic circulation are beneficial. Drug delivery to the lungs provides advantages over oral administration of active agents such as proteins and peptides, which are sensitive to enzymatic deactivation or degradation in the gut. In addition, absorption through the lungs into the systemic circulation is more effective in reaching target tissues, bypassing the liver, which is the site of metabolic action of most drugs delivered by injections and other routes of administration. The potential for delivering many other compounds through the lungs for systemic administration, ranging from peptides and proteins to small molecules often requires numerous studies and approaches depending on the delivery system used.

[0007] For pulmonary delivery, medicines are often formulated into a liquid or dry powder format so that they can be aerosolized and inhaled by patients. Aerosolization is achieved by delivery devices such as inhalers, atomizers, and nebulizers, which convert a payload of the liquid or dry powder formulation into a respirable dispersion. The dispersion is comprised of particles suitably small for navigating the airway and depositing in the lung. Particles that are too large carry excessive inertia, impact the back of the throat, and are swallowed. Particles that are too small can be exhaled and never deposit in the lung.

[0008] Early development work on drug formulations often requires non-clinical testing. This may involve small animals, including, mice, rats and other rodents, wherein drug delivery, exposure and the resulting effects can be studied before

progressing to large animals and into human administration studies. Pharmacokinetic and pharmacodynamic effects along with adverse events can be assessed using an animal model to help progress or halt development of candidate drug formulations. It is therefore, extremely important in evaluating a potential drug that the delivery of the formulation being tested is consistent to ascertain with more accuracy the envisioned delivery in humans. For example, if the drug is intended for delivery in a single inhalation using an inhaler together with a dry powder formulation, then the small animal testing should approximate the envisioned approach in humans.

[0009] Current model methodologies used to assess delivery and efficacy of drugs for pulmonary delivery, include liquid instillation or dry powder insufflation. These methods have been developed by researchers to enable placement of candidate drug formulations directly into the lung. The methods involve syringe-like systems such as the PennCentury DP-4, wherein an elongated blunted cannula, dry powder chamber and syringe are used to disperse the contents of the chamber into the animal's lungs. To perform the insufflation, the animal is lightly anesthetized and intubated to insert the device cannula past the vocal cords and into the trachea just before the carina, the tracheal bifurcation leading into the bronchi. Oftentimes, a laryngoscope is used to help the researcher guide the cannula during the insertion step. The syringe barrel is then depressed forcing the contents, either liquid, suspension, or powder out of the chamber, down the cannula, and into the animal's lung. The air volume to discharge the powder from an insufflator is typically between 1.0 to 5.0 mL depending on the animal species. Using this equipment, a valve feature within the powder chamber prevents air flow and the subsequent aerosolization until a minimum threshold pressure is achieved. Accordingly, researchers exert significant manual force to depress the syringe plunger during activation thereby aerosolizing the contents of the chamber with minimal air volume.

[0010] Two major challenges are encountered with the aforementioned techniques. The first challenge is one of timing delivery of the drug during the breathing cycle. Discharge of powder into an animal during exhalation results in sub-optimal delivery as the contents can be blown back and are not delivered to the test subject. With powder delivery, powder blow back condition results in exhalation of drug, making it impossible

to estimate the magnitude of drug delivery and confounding any measurable effects by the drug. Manual discharge of powder or liquid to avoid blow back is difficult in animals with high respiratory rates and or small lung capacity, for example, in mice having typically, 90 breaths per minute. The second challenge is repeatability and/or consistency. Current technology requires a minimum pressure to disperse a drug formulation. The devices allow for a range of pressures above that minimum which affect both the quality and consistency of the dispersion. Airflows occurring with the minimum required pressure may produce an aerosol discharge with large particle sizes that are not able to be inhaled deep into the lung. Large sizes are prevented from navigating deep into the lung because inertial forces become too large forcing the drug laden particles into the upper airway branches of the lung. Conversely, airflows occurring with higher applied pressures may produce aerosol discharges with far greater quality. Particle sizes within these emitted aerosols will likely be reduced and therefore will have a much greater likelihood of depositing deeper in the lung. The dependence of consistency on the applied syringe plunger pressure is also difficult to overcome. Instillation and/or insufflation studies typically involve multiple animals which can lead to variations in drug delivery from animal to animal if procedures are manually executed. Sources of variation in the drug delivery make assessment of drug effect more difficult to interpret.

[0011] Dosing reproducibility during experiments requires that the drug formulation be delivered to the subject with consistent and reproducible results. Therefore, the inventors have seen the need to design and manufacture an apparatus, system, and method to overcome the problems encountered with standard apparatuses and procedures currently used.

SUMMARY

[0012] A drug delivery system is provided comprising an apparatus and a method for delivering a drug composition, including aerosolized particles to the lungs are disclosed.

[0013] The apparatus comprises devices configured for measuring and recording an animal's breathing cycles; ascertaining the intervals of the breathing cycles and

delivering an aerosol at a predetermined interval relative to an animal's breathing, in particular during an inhalation. The apparatus can comprise one or more sensors selecting from a variety of sensors, including, but not limited to accelerometers, microphones, strain gauges and transducers.

[0014] In one embodiment, computer algorithms specific to the sensors can then characterize and quantitate the animal's breathing pattern and determine when to trigger the insufflation in order to synchronize delivery with a natural inhalation maneuver. In one embodiment, delivery of dose composition can also be synchronized with different portions of the breathing cycle prior to or during an inhalation. The duration of the inhalation can also be checked, and assessed to determine the extent of delivery relative to the start and end of the inhalation. In one embodiment, active monitoring of the animal's breathing also generates data on duration of inhale/exhale, regularity of breathing, and other characteristics of the breathing cycle. In this and other embodiments, the apparatus is provided with an automated driving mechanism that displaces air through the insufflation device, by adapting an electromechanical device. In one embodiment, a linear solenoid can be used to displace a driving pump's piston, which ensures repeatable driving force and results in repeatable discharge flow rates.

[0015] In one embodiment, an apparatus is provided comprising:

a first device comprising a platform comprising an area for positioning an animal and configured to hold an animal in place and comprising an adjustable strap adapted with at least one sensor which detects movement of distension of the animal's thorax and/or abdomen due to breathing; said sensor generates a signal and communicates the signal to a microprocessor for analysis; and mounting means, including a stand for securing to said platform;

a second device comprising a solenoid, a syringe pump and a powder reservoir; wherein said solenoid is actuated by an onboard relay output system to pressurize the syringe pump; said second device further comprising a computer interface comprising a programmable algorithm which detects an animal's breathing pattern and said solenoid is actuated to pressurize the syringe pump at a predetermined interval during an inhalation to release a powder plume from the powder reservoir.

[0016] In one embodiment, the first device can further comprise a second sensor, which can detect sound generated from the animal's breathing cycles. In this and other embodiments, the apparatus can also comprise one or more modules comprising a relay board for relaying an output signal, such as an automated on and off switch; and a data acquisition board. In this embodiment, a first sensor communicates a first set of input signals to a first microprocessor configured with a data acquisition board which captures the input signals from the sensors, processes and analyzes the first set of signals in the first device and continuously streams to a computer and communicates with a relay board to actuate the solenoid and pressurize the syringe to discharge a powder contained in the powder reservoir at a predetermined interval.

[0017] In one embodiment, the first device comprises an adjustable cantilevered arm on which a transducer is mounted and can be positioned in the desired position on an animal to best measure physiological changes associated with breathing, such as diaphragm distention.

[0018] In a particular embodiment, a drug delivery system is provided comprising: an air pump adapted with a solenoid; an insufflation or instillation device adaptable to said air pump and comprising a chamber for containing a drug composition and a cannula; one or more sensors which can detect signals from breathing cycles of an animal; and a data acquisition board comprising an executable algorithm analyzing and transmitting signals from said one or more sensors, wherein the executable algorithm contains instructions to actuate the solenoid at a predetermined interval of a breathing cycle of the animal. In an example embodiment, the acquisition board can process the signals from the sensors within a computer, which makes the system modular, or can be part of a microprocessor built-in with the solenoid. In one embodiment, the animal is anesthetized and the system can have at least two sensors, including an accelerometer and a microphone.

[0019] In further embodiments, a method for insufflating an animal, including for example dogs, cats, monkeys, and rodents such as a mouse or a rat is disclosed. In a particular embodiment, the method comprises: anesthesizing an animal; positioning one or more sensors on or near the animal in the insufflation apparatus; detecting and

analyzing the animals breathing cycles and administering a dose of a test composition at the inhalation interval of said animal. In an alternate embodiment, the method can also be used to instill a solution, a suspension, and/or a vapor to an animal.

[0020] In a particular embodiment, detecting and analyzing the animal's breathing cycles comprises positioning one or more sensors, such as an accelerometer, a microphone, or a transducer on or near the animal, which sensor(s) can detect signals from the animal, and transmit the signals to a data acquisition board, through which signals are analyzed and evaluated using an algorithm executable by, for example, a microprocessor on board a computer, or a programmable logic controller (PLC).

[0021] In one embodiment, signals from one or multiple sensors including, but not limited to microphones, thermocouples, strain gauges, accelerometers, and the like are used to optimally position the sensor(s) relative to the animal. In this embodiment, positioning information is relayed via a computer interface in which an algorithm detects the sensor output. An algorithm determines if the position is acceptable using sensor specific criteria, for example, validity of signal to noise, peak detection, slope detection, baseline noise and the like. The positioning of the sensor can occur manually by an operator or automatically using computer controlled, including motors and pneumatics, and sensor feedback.

[0022] In one embodiment, the method comprises, positioning an animal to be tested to an accessible area, for example, strapping the animal to a platform comprising an adjustable belt comprising one or more sensor(s), including an accelerometer, a transducer and/or a microphone; positioning the one or more sensor(s) to detect one or more signals generating from the animal's breathing cycles; actuating a power source and setting the accelerometer to detect a predetermine number of input signals to characterize the breathing pattern of the animal; and delivering an aerosolized powder plume to the animal during an inhalation. In a specific embodiment, the method comprises, determining the animal's breathing rate and inhalation intervals; and delivering a dose of an aerosolized composition at an inhalation interval. In some embodiments, the animal can optionally be strapped to the platform comprising a

restraining area. In some embodiments, the adjustable belt can comprise an elastic material.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] FIG. 1 depicts a schematic representation of an embodiment of the drug delivery system or apparatus.

[0024] FIG. 2A depicts a schematic representation of the apparatus embodiment of FIG.1, illustrating the details of a platform embodiment adapted with a strap containing an accelerometer for positioning on an animal. FIG. 2B depicts FIG. 2A showing a balloon mouse simulator adapted to the apparatus for *in vitro* testing studies.

[0025] FIG. 3 depicts a schematic representation of an embodiment device component of the apparatus of FIG. 1 showing a solenoid and syringe pump system.

[0026] FIG. 4 depicts a schematic representation of an embodiment herewith depicting a flow chart illustrating the functional systems associated with the apparatus of FIG. 1.

[0027] FIG. 5 depicts an embodiment of the insufflation device for adapting to the apparatus illustrated in FIG. 1 and containing a drug chamber or reservoir and showing a cannula for intubating an animal and delivering a powder dose.

[0028] FIG. 6A is a photograph of platform section of the embodiment illustrated in FIG. 1 showing its components part and an attached balloon simulation adaptor is showing in FIG. 6B to represent a small animal.

[0029] FIG. 7 is a computer screenshot showing an output signal from an embodiment apparatus which signal was obtained using a balloon connected to a pump (FIG 6B setup) to simulate breathing by mimicking inflate and deflate such as during a breathing cycle for a small rodent and assembled into the device.

[0030] FIG. 8 is a schematic representation of an alternate platform embodiment of the apparatus embodiment of FIG. 1, depicting a movable cantilevered arm containing a linear positioning sensor for use with small experimental animals.

[0031] FIG. 9 is a schematic representation of a modified top view of the platform embodiment in FIG. 8 showing the positioning of the cantilever moveable on a stage.

[0032] FIG. 10 is schematic representation of the functional components of the operating system of the drug delivery apparatus.

[0033] FIG. 11 is a schematic representation of the hardware communication system of an embodiment of the herein described apparatus.

[0034] FIG. 12 is schematic representation of the insufflation sequence using an example embodiment apparatus for use with an experimental animal.

[0035] FIG. 13 is a computer screenshot showing an output signal generated from data obtained from an insufflation study with an embodiment apparatus in use during an insufflation of a Sprague Dawley rat as exemplified in FIGs. 8 and 9.

DETAILED DESCRIPTION

[0036] In embodiments disclosed herein, there is disclosed an apparatus, a system, and a method for delivering drugs to an animal by insufflation.

[0037] In an exemplary embodiment illustrated in FIGs. 1-7, there is disclosed an insufflation apparatus with an interactive system and methods for administering intratracheal aerosols to small animals, including mice and rats. The apparatus 10 can be used to deliver aerosols in dry powder, suspension, or in liquid form. In one embodiment, the apparatus 10 can be used to insufflate, for example, mice, or Sprague-Dawley rats with dry powder aerosols for delivering test drug formulations in research and development, and for use in small animal practice in veterinary medicine, including, dogs, cats, guinea pigs, hamsters, monkeys, and the like.

[0038] In this embodiment and illustrated in FIG. 1, the insufflation apparatus 10 comprises a stand, a platform 14 (FIGs. 2A and 2B) for positioning an animal, including a mouse or a rat, a movable adjustable retainer 9, a data acquisition system (not shown), a strap 13 comprising a sensor 15 such as an accelerometer and/or microphone, a solenoid 17 adapted to a small volume air pump 16 (FIG. 3), and a unit-dose reusable insufflation device (FIG. 5) to disperse pre-metered masses of powder from a powder reservoir adapted with a cannula 28. In this embodiment, the apparatus

comprises a sensor 18 such as microphone and an accelerometer 19 to monitor breathing signals, including, sound signals, air flow, chest or diaphragm distention signals, and the like. In some embodiments, the apparatus may comprise a single sensor or multiple sensors, which can be used to detect different types of signals from the animal and include, but are not limited to, transducers, strain gauges, pressure gauges, or thermistors.

[0039] FIG. 4 is a schematic representation of an embodiment herewith, and illustrates an example of the physical and/or electronic interactions between various components of apparatus 10, wherein apparatus 10 comprises two sensors, a first sensor which can be an accelerometer 19 for detecting distension of the abdomen, and a second sensor, for example, a miniature microphone 19 for detecting breathing sounds generated from the breathing cycles of an animal. In this embodiment, both types of signals generated from the first sensor 18 and second sensor 19 are relayed to a data acquisition board 22, which receives the different types of signals and streams them to a software interface comprising real-time breathing monitoring analysis and processing capabilities of an animal's breathing cycles. Apparatus 10 is controlled with software algorithms to correlate characteristic electrical signals from the sensors to the animal's breathing. FIG. 4 also shows that output signals from data acquisition board 22 are sent to an automated pump controller 26 to actuate solenoid 17 adapted to syringe pump 16 to automatically actuate the solenoid when an insufflation maneuver is needed to administer a dose during a test or treatment procedure.

[0040] In this and other embodiments, the actuation of the air pump 16 by solenoid 17 can also be controlled to exert constant or varying force levels based on selection of hardware and software algorithm features. In one embodiment, the trigger of the automated air pump 16 is controlled by an executable algorithm and can then be actuated at any point in the breathing cycle. This will allow for triggering of the pump offset from a feature within the breathing cycle or in a manner predictive of inhale, exhale, or other marker in the breathing cycle. In this embodiment, the optimal actuation is expected to be upon start of an animal's inhalation period. In one embodiment, aerosol delivery will occur in a single or multiple short bursts and during a

single, or multiple consecutive, or non-consecutive inhalations depending on the dose and the animal.

[0041] In an exemplary embodiment as disclosed in FIGs.1 through 5, FIG. 1 illustrates an animal stand 12, 14, and a solenoid 17 driven hand pump 16. FIG. 2 provides a close-up of the animal stand pictured in FIG. 1 comprising: platform 14, an animal retaining adjustable bar device 9 and animal strap 13 comprising sensor 19. In this particular embodiment, animal stand 14 comprises a microphone slide 20 and bracket 21, microphone 18, hanging wire and neck support post 9, adjustable strap 13 mounts and the strap with accelerometer 19 mounted to it. In this embodiment, the rat is meant to hang from wire 9 by its incisors, and the neck post provides support and alignment for the rear of the animal's neck. The strap 13 and accelerometer 19 are designed to be positioned over the diaphragm on the chest-abdomen area to detect the animal's breathing cycles. Microphone 18 is positioned near the animal's nose, to be able to monitor its breathing cycles. Data is collected from microphone 18 and accelerometer 19 by analog ports on data acquisition board 22, and an executable algorithm is run which converts both the accelerometer and microphone signals into information describing the animal's breathing pattern.

[0042] FIG. 2B is the embodiment of FIG. 2A comprising an adaptor for in vitro studies of the insufflation apparatus and comprising a balloon positioned in the center of the adaptor and connected to an air pump which inflates the balloon at predetermine intervals to simulate breathing patterns of a small animal. In one embodiment, the air pump is automatically controlled by a computer program.

[0043] Figure 3 is a drawing of an embodiment, which provides a close-up or more detailed view of the automated pump embodiment in FIG. 1. The automated air pump assembly 16 comprises an adjustable spring return hand pump, a solenoid mounting cylinder 17 and a solenoid 24. In one embodiment, the discharge volume of hand pump 16 can be adjusted to volumes less than the animal's regular or tidal breathing volume to reduce over-pressurizing the animal's lung during an insufflation procedure. For a small animal, the air pump can discharge volumes less than 5 ml, less than 3 ml, less than 2 ml, or less than 1 ml, depending on the animal to be insufflated. In one

embodiment, the volume of pressurized air delivered by syringe pump 16 is from about 0.25 ml to about 1.5 ml, or from about 1 to 1.5 ml. In some embodiments, larger volumes greater than 3 ml of air can be delivered depending on the animal and the size of the dose to be administered. In one embodiment, the syringe pump is driven by solenoid assembly, which generates results in a repeatable manner and consistent force profile, since force is applied in a consistent manner. The automated air pump assembly in use provides a reduction in air volume required in typical insufflators to deliver the contents of a dose from the insufflation device, thus limiting dose content blow back post insufflation.

[0044] FIG. 4 specifically depicts a block diagram showing the sequence required for automation. In this embodiment, the apparatus 10 can be activated by pushing the run button on the software interface. The actuation trigger of apparatus 10 begins the collection of signals from both the accelerometer 19 and microphone 18. The analog signal from accelerometer 19 is processed before data acquisition board 22. Analog signals from each sensor 18, 19 are transmitted to the data acquisition board 22, which then transmits the signals to the software in a computer or PLC for additional processing and real time analysis. Using the software set of instructions, the signals from each sensor 18 and 19 are converted into signals describing the breathing pattern of the animal with relevant parameters, for example, duration of inhale, duration of exhale, breaths per minute, change in breathing rate, tidal volume, and the like. The computer software 29 instructions enables the rapid identification of the start of the animal's inhalation maneuver, and thus allows for the actuation of the pump and discharge of the drug liquid, suspension or powder prior to the end of a single inhalation. In some embodiments, if the quantity of drug exceeds a volume that can be administered in one inhalation, it is possible to administer the drug by a predetermined number of consecutive inhalations, or at predetermine intervals that can skip one or more inhalations.

[0045] As previously stated, the insufflation system can be used to administer liquids, suspensions and dry powders by intratracheal insufflation. FIG. 5 depicts an embodiment of a single dose reusable insufflation device 30, which can be adapted to apparatus 10 in series with air pump 16 for use with a small animal such as a rodent

insufflation system. In this embodiment, the insufflation device 30 can be designed to administer various types of composition, including dry powders and comprises a substantially cylindrical body in the form of a syringe 30. In one embodiment, insufflation device 30 can connect to automated air pump 16 by a short tube 17a. The device can be made of materials, including metal to alleviate static effects on the drug composition being insufflated. The insufflation device 30 further comprises a chamber 15 with one or more valves for containing a powder composition. In alternate embodiments, the chamber 15 can comprise a reservoir for liquids or suspensions for use in instillations. The tip of the insufflation device 30 comprises a blunt cannula 28, which is used to directly intubate an anesthetized animal. Once the animal is intubated, the blunt end of the cannula is for positioning through the animal's mouth until it reaches near the carina of the tracheal region of the respiratory tract to ensure lung deposition of the drug composition to be insufflated. FIG. 5 also illustrates the insufflation device 30 further comprising an air inlet port 32 for allowing air into the pump upon retraction of the piston of the syringe pump 16; and one or more valves (not shown) to regulate air intake and powder containment in chamber 15 prior to delivery. Moreover, chamber 15 can be remove from the short tube 17a with or without cannula 28 to provide replacement of individual dosing units.

[0046] In an alternate embodiment, the insufflation apparatus comprises a platform 40 for use with animals that may not need to be strapped or restrained. In this embodiment shown in FIGs. 8 and 9, platform 40 is mounted on a stand 42 comprising base 44, support beams 46, 46' adapted with hinge 48 configured to hold platform 40 and a shaft 45 to hold and support an air pump; solenoid and insufflation device. In this embodiment, platform 40 supported by a stand 43 configured on base 44 and it is designed to comprise an adjustable stage assembly 50 comprising a cantilevered arm 52 that can be moved to different positions depending on the size of the animal to be insufflated. In one embodiment, arm-like structure 52 is connected to platform 40 through a joint to pivot, rotate and or extend, and can be placed over the abdomen of the animal. FIG. 9 is a modified top view of a portion of the apparatus illustrated in FIG. 1 adapted with a platform as shown in FIGs. 8 and 9. As seen in FIGs. 8 and 9, sensor 54 comprises a transducer in particular, linear sensor pin 54, including, pin 56; wire

posts 58, 58'; wire 60 for holding, for example, a rat by its incisor teeth; and screw 62 for adjusting or moving the stage to position and adjust the sensor on an animal. In this embodiment, screw 62 moves the cantilevered arm up and down on a vertical plane. In some embodiments, platform 40 can be adapted with a robotic arm comprising a plurality of sensors, including sensor 54, microphones, thermistors, transducers, or an accelerometer.

[0047] In some embodiments, platform 40 can further include a nose cone 57 that can removably attach to the top end of the platform. Nose cone 57 can serve as a mount allowing tubing to be passed through in order to keep an animal anesthetized.

[0048] In an alternate embodiment, the sensor on the cantilevered arm can comprise an accelerometer or other types of sensing device. The sensor 54 can be placed at the distal end of the arm for monitoring breathing signals from the animal. FIG. 8 depicts an embodiment with the swivel arm-like component of the insufflation apparatus. In an alternate embodiment, platform 40 comprises a robotic arm comprising an accelerometer.

[0049] FIG. 10 is schematic representation of the functional components of one operating system of the drug delivery apparatus. As indicated in FIG. 10, input signal 70 generated from an animal is detected by sensor 74 once the program has been initiated to position the sensor 72. This signal is transmitted from the sensor to a data acquisition board and processed in a computer. If the sensor 76 is determined to have proper position, the signals are processed and as output as baseline breathing data 78. If the sensor is not properly placed on the animal, the sensor is adjusted 79 until acceptable baseline signals are obtained. When baseline breathing signals are properly detected, dosing can begin 80. Sensor output is detected 81 by on board system 82 and determines if the signals indicate the start of inhalation. If the signals are not from an inhalation the system continues monitoring until it detects an inhalation upon which the system can trigger actuation of the solenoid to activate the air pump 84. In one embodiment, the insufflation system can be set for a single dose delivery 86. If multiple dosing or repeated doses are to be administered, the system queries if it is the last trigger 86. If it is not the last trigger, the system will continue to detect inhalation signals

until all doses are delivered and the output data 88 is displayed on a screen, printed, or saved in the microprocessor or computer system.

[0050] FIG. 11 is a schematic representation of the hardware communication system of an embodiment of the claimed apparatus. Sensor 90 which can be a microphone, accelerometer, thermistor, or transducer sends signals to a data acquisition board 91, which can be part of a microprocessor or a computer module. Signals from the data acquisition board 91 are processed and analyzed using a processing algorithm 92, which detects positioning of the sensor and/or dosing, and also communicates output regarding the breathing patterns of the animal and about proper positioning of sensor and to computer 95. Processing algorithm 92 also analyzes the inhalation information 94 from the animal and if an inhalation is detected, it directs the information to the data acquisition board 96 for further action. The data acquisition board determines if a trigger of an insufflation is required and if so it directs the relay board 97 to actuate the solenoid 98 and activate the air pump to initiate an insufflation as the animal begins an inhalation.

[0051] FIG. 12 is schematic representation which summarizes the sequence of steps that are needed to performing an insufflation study using an example embodiment apparatus for use with an experimental small animal, for example, a rat or a mouse.

[0052] The preceding disclosures are illustrative embodiments. It should be appreciated by those of skill in the art that the techniques disclosed herein elucidate representative techniques that function well in the practice of the present disclosure. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments that are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

EXAMPLE 1

Monitoring and Delivering a Measured Dose of a Powder Composition:

[0053] The photographs in FIGs. 6A and 6B depict an actual apparatus set up intended for use with a small animal, in this example, the apparatus was designed for use with rodent such as a rat or a mouse. FIG. 6A depicts the insufflation system

prototype consisting of a plexiglass and metal stand and a platform. As shown in FIGs. 6A and 6B a portion of the stand is visible, consisting of a Lucite platform attached to a mounting means having supports for holding the platform. For testing purposes, the insufflation apparatus herewith is illustrated using a balloon which was mounted underneath the accelerometer strap to simulate the displacement motion of the abdomen/thorax of a rat or mice during breathing. The balloon is secured to the platform and for undergoing a simulation insufflation procedure. The balloon has been positioned in the same location as the abdomen of the animal that would be in the process of being insufflated. This configuration is to serve as a test which allows to assess the signal captured by the accelerometer mounted at the center of the strap. The balloon is connected to a pressurized air source and a three way valve and can thus be inflated and deflated periodically to mimic the breathing pattern of a small animal.

[0054] The screenshot in FIG. 7 acquired from an experiment with a balloon shows the control interface with a plot of the data collected from the accelerometer and displayed on a screen. The signal is characterized by a baseline when the balloon is at rest. Upon rapid inflation and deflation of the balloon, the accelerometer measures a rapid changing oscillating signal. The system is then set to actuate the solenoid in the second device, an air pump (not shown) pressurizes the syringe pump to discharge a powder from the powder reservoir at a predetermine interval during a simulated inhalation.

EXAMPLE 2

Insufflation experiments with rats

[0055] Sprague-Dawley rats were used in these experiments. Rats were anesthetized, intubated and monitored using the insufflation assembly shown in FIGs. 5 and 8, using the method as described in FIG. 12 and 5 mg of dry powder compositions per kilogram of weight of rat. Administration of the dose to each rat was triggered by the system during natural inhalation as detected by the system. Data collected from these experiments show that the process for intubation and insufflation was achievable for the delivery of doses of neutron activated cerium dioxide (NM-212, Specific

Activity=5.7μCi of ^{141}Ce/mg CeO_2) to the rats during inhalations in a consistent manner data not shown). Table 1 illustrate data obtained from this study.

Table 1: Inhalation characteristics during insufflation.

		average		
animal ID	**# of inhalations**	**inhalation duration (s)**	**inhalation cycle (s)**	**Inhalations per minute**
rat 25	10	0.260	1.275	47.1
rat 26	10	0.169	1.524	39.4
rat 27	10	0.226	1.224	49.0
rat 28	10	0.108	0.685	87.5
rat 29	10	0.096	0.863	69.5
rat 30	8	0.274	1.357	44.2
rat 31	9	0.182	1.041	57.6
rat 32	10	0.115	0.682	88.0
rat 33	10	0.140	0.867	69.2
rat 34	8	0.216	0.897	66.9
rat 35	10	0.156	1.255	47.8
rat 36	9	0.062	1.111	54.0
	average	0.167	1.065	56.3

[0056] The data in Table 1 shows that the breathing cycles detected by the apparatus herein are greater than 0.5 seconds. Specifically, the data shows the rats breathing cycles detected indicated that the rats were breathing at intervals between 0.68 and 1.52 seconds with inhalations lasting from about 62 to about 300 milliseconds.

[0057] FIG. 13 is a computer screenshot showing an output signal generated from data obtained from an insufflation study with an embodiment apparatus in use during an insufflation of a Sprague Dawley rat describe herewith. As seen in FIG. 13, each breathing cycle for the rat is shown from valley to valley in a real-time plot of the data collected with a linear position sensor as described in FIGs. 8 and 9.

[0058] The preceding disclosures are illustrative embodiments. It should be appreciated by those of skill in the art that the techniques disclosed herein elucidate representative techniques that function well in the practice of the present disclosure. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments that are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

[0059] Unless otherwise indicated, all numbers expressing quantities of ingredients, properties such as molecular weight, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in the specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained by the present invention. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques. Notwithstanding that the numerical ranges and parameters setting forth the broad scope of the invention are approximations, the numerical values set forth in the specific examples are reported as precisely as possible. Any numerical value, however, inherently contains certain errors necessarily resulting from the standard deviation found in their respective testing measurements.

[0060] The terms "a," "an," "the" and similar referents used in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. Recitation of ranges of values herein is merely intended to serve as a shorthand method of referring individually to each separate value falling within the range. Unless otherwise indicated herein, each individual value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention otherwise claimed. No language in the specification should be construed as indicating any non-claimed element essential to the practice of the invention.

[0061] Groupings of alternative elements or embodiments of the invention disclosed herein are not to be construed as limitations. Each group member may be referred to and claimed individually or in any combination with other members of the group or other elements found herein. It is anticipated that one or more members of a group may be

included in, or deleted from, a group for reasons of convenience and/or patentability. When any such inclusion or deletion occurs, the specification is deemed to contain the group as modified thus fulfilling the written description of all Markush groups used in the appended claims.

[0062] Certain embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Of course, variations on these described embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventor expects skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

[0063] Furthermore, numerous references have been made to patents and printed publications throughout this specification. Each of the above-cited references and printed publications are individually incorporated herein by reference in their entirety.

[0064] Specific embodiments disclosed herein may be further limited in the claims using consisting of or and consisting essentially of language. When used in the claims, whether as filed or added per amendment, the transition term “consisting of” excludes any element, step, or ingredient not specified in the claims. The transition term “consisting essentially of” limits the scope of a claim to the specified materials or steps and those that do not materially affect the basic and novel characteristic(s). Embodiments of the invention so claimed are inherently or expressly described and enabled herein.

[0065] In closing, it is to be understood that the embodiments of the invention disclosed herein are illustrative of the principles of the present invention. Other modifications that may be employed are within the scope of the invention. Thus, by way of example, but not of limitation, alternative configurations of the present invention may

be utilized in accordance with the teachings herein. Accordingly, the present invention is not limited to that precisely as shown and described.

We claim:

1. A drug delivery system, comprising:

air pump adapted with a solenoid,

a drug delivery device adapted to said air pump and comprising a cannula and a chamber for containing a drug composition;

at least one sensor for detecting breathing cycles of an anesthetized animal;

a data acquisition board comprising an executable algorithm for analyzing and transmitting signals from said one or more sensors and determining and displaying an animal's breathing pattern, wherein said executable algorithm contains instructions to actuate said solenoid at a predetermined interval of a breathing cycle of said anesthetized animal.

2. The system of claim 1, including a second sensor configured to detect an animal's breathing.

3. The system of any of the preceding claims, wherein the at least one sensor is an accelerometer, a microphone, a thermistor, and/or a transducer.

4. The system of any of the preceding claims, wherein the at least one sensor is a microphone.

5. An apparatus, comprising:

a first device comprising a platform comprising an animal positioning area comprising an adjustable strap with at least one sensor which detects distention of the animal's abdomen and/or thorax due to breathing, generates an input signal and communicates the input signal to a microprocessor for analysis;

a second device comprising a solenoid, a syringe pump and a powder reservoir; wherein said solenoid is actuated by an onboard relay output system to pressurize the syringe pump; and wherein said second device further comprises a computer interface comprising a programmable algorithm which detects, analyzes and sends instructions of

an animal's breathing pattern and actuates said solenoid to pressurize the syringe pump at a predetermined interval during an inhalation.

6. The apparatus of claim 5, further comprising a mounting means for securing said platform.

7. The apparatus of claim 6, wherein said first device further comprises a second sensor, which is configured to detect an animal's breathing.

8. The apparatus of any of the preceding claims, wherein the at least one sensor is an accelerometer, a microphone, a thermistor, and/or a transducer.

9. The apparatus of any of the preceding claims, wherein the at least one sensor is a microphone.

10. An insufflation method comprising:

positioning an animal in an insufflation apparatus comprising an automated air pump syringe adapted with a solenoid;

placing one or more sensors on or near the animal to detect breathing signals of said animal, wherein the sensors are configured to detect and transmit the breathing signals and communicate with a data acquisition board;

analyzing the breathing signals from the animal's breathing cycles to determine and analyze the animal's breathing rate and cycles in real-time using a microprocessor with an executable algorithm, and

administering a dose of a test composition at an inhalation interval by actuating the solenoid to generate a predetermined force at a predetermined interval of an inhalation of the animal's breathing cycle.

11. The method of claim 10, wherein the insufflation apparatus further comprises an insufflation device comprising a cannula and a chamber to contain a drug composition.

12. The method of claim 10, wherein the one or more sensors is an accelerometer, a microphone, a thermistor, or a transducer.

13. The method of claim 10, wherein the one or more sensor is a microphone.

14. The method of any of the preceding claims, wherein the animal is anesthetized.

15. The method of any of the preceding claims, wherein actuating the solenoid is carried out from signals from a computer interface comprising a programmable algorithm.

16. The method of any of the preceding claims, wherein actuating the solenoid generates air pressure in the air pump syringe which discharges the dose of the test composition.

17. The method of any of the preceding claims, further comprising intubating the animal with the cannula from the insufflation device.

18. The method of claims 10-17, wherein placing of the one or more sensors on or near the animal is automated.

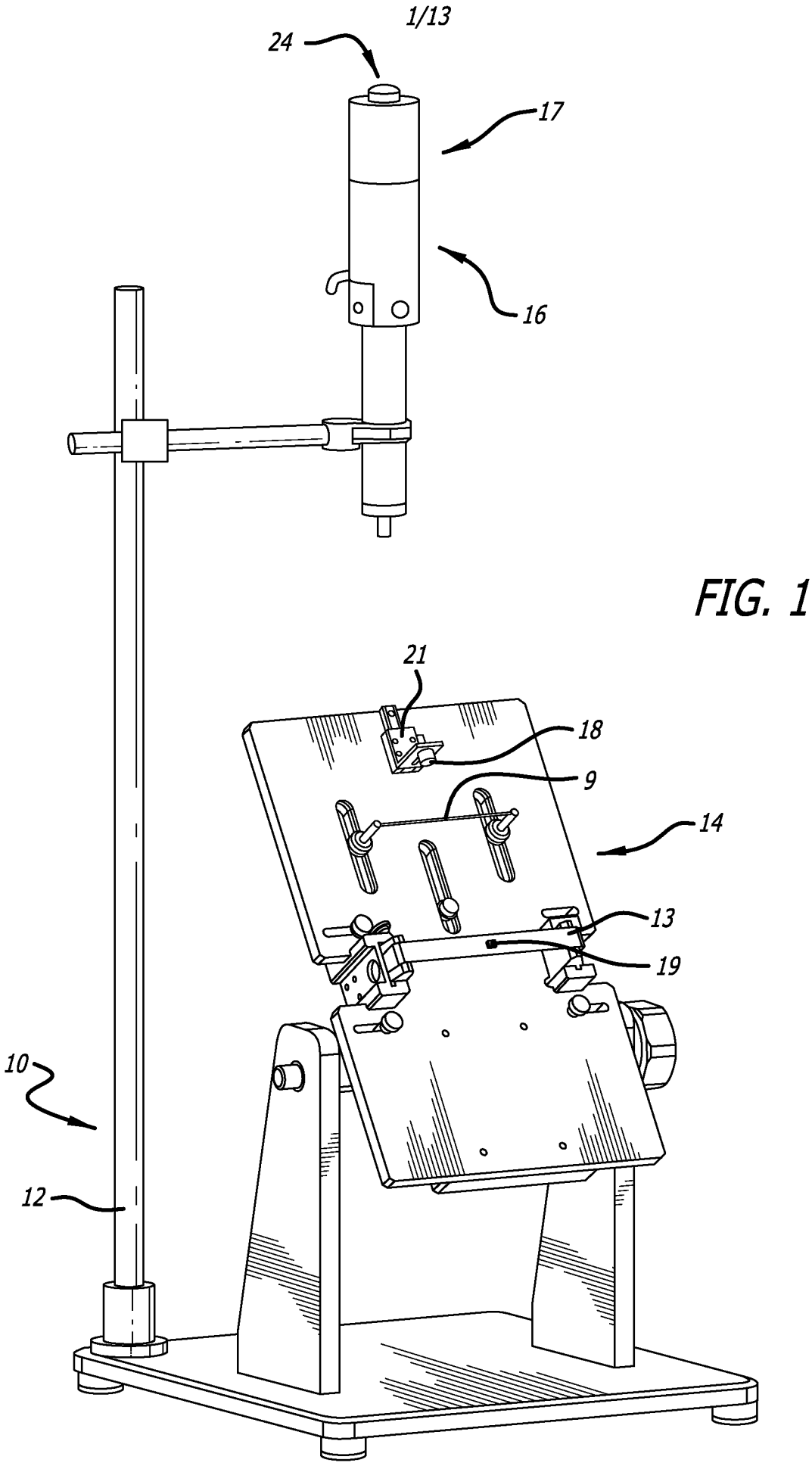


FIG. 1

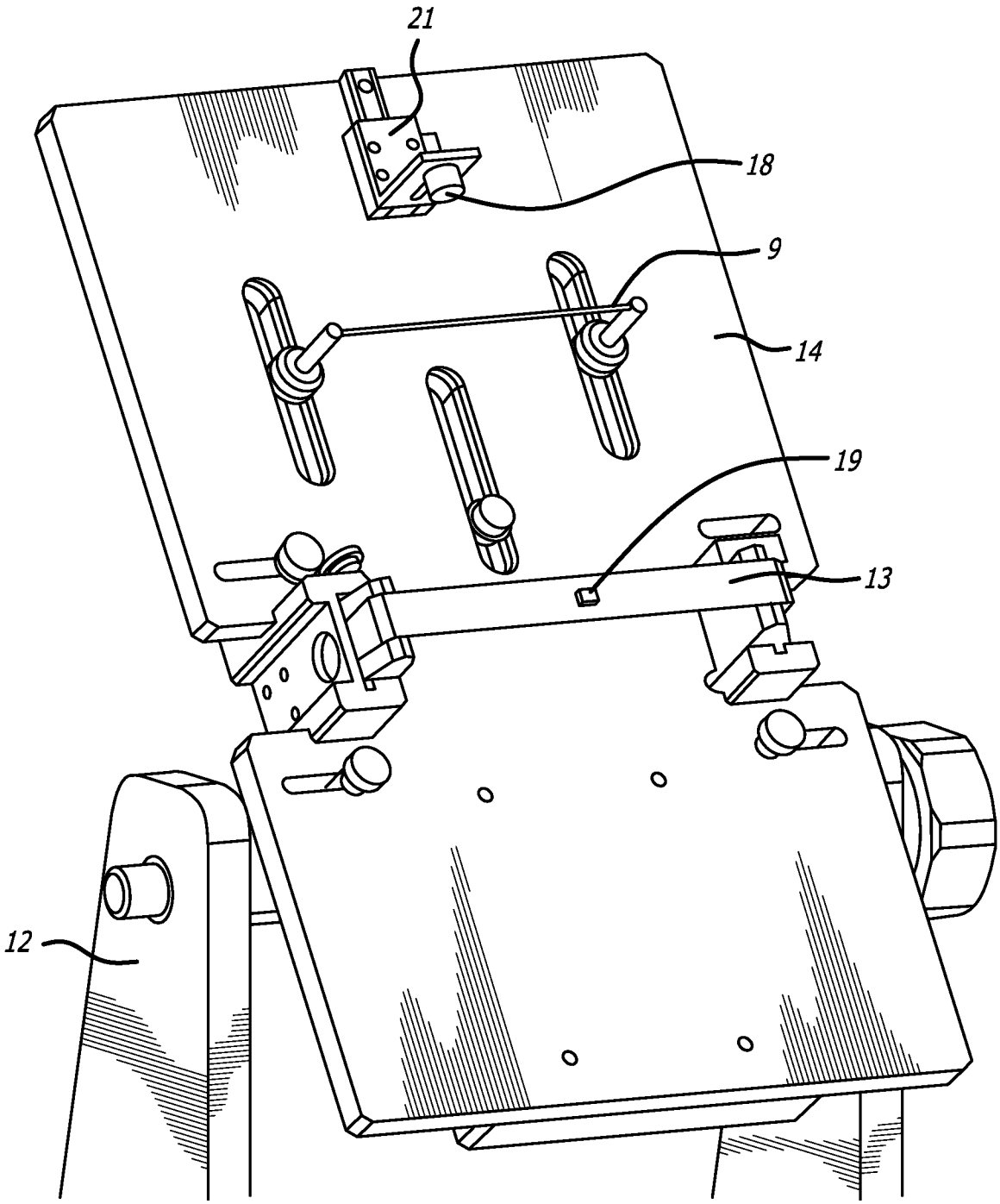


FIG. 2A

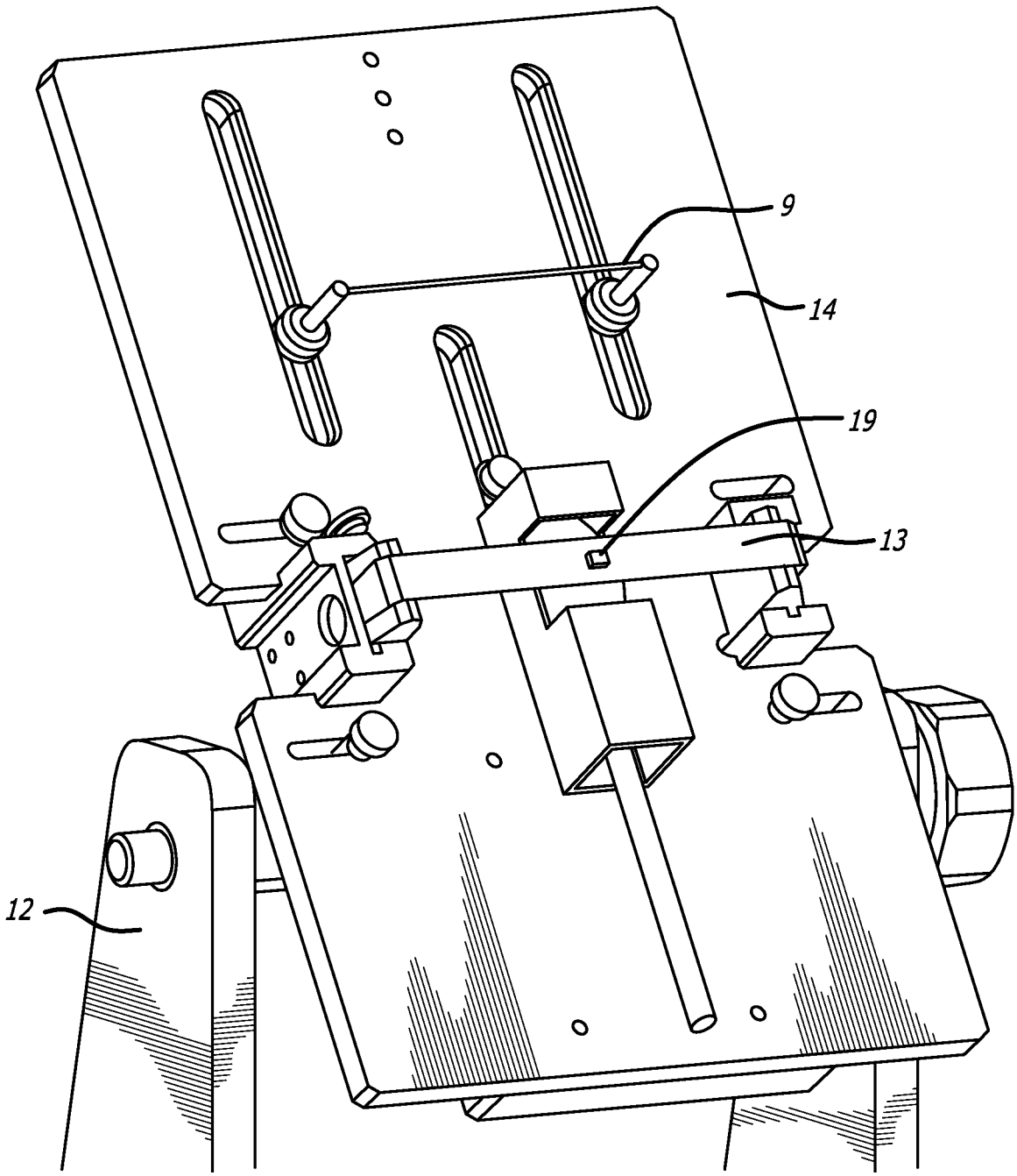


FIG. 2B

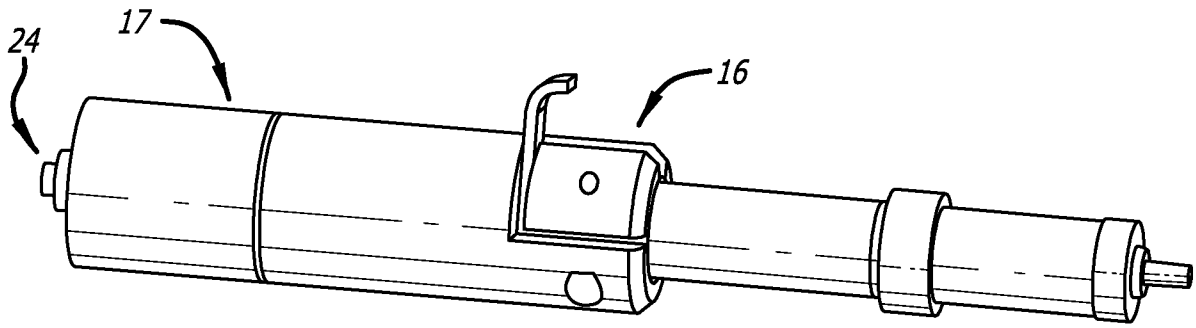

24
17
16

FIG. 3

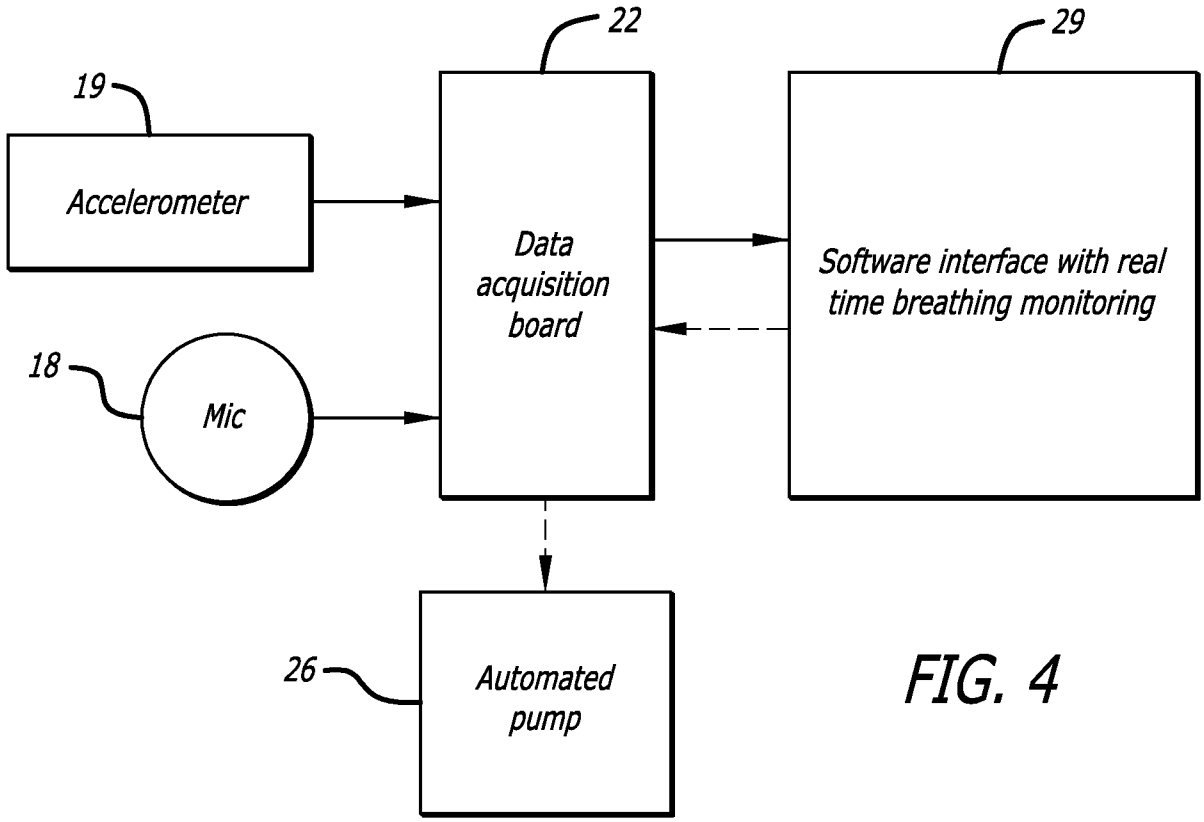

22
29
19
Accelerometer
Data acquisition board
Software interface with real time breathing monitoring
18
Mic
26
Automated pump

FIG. 4

FIG. 5

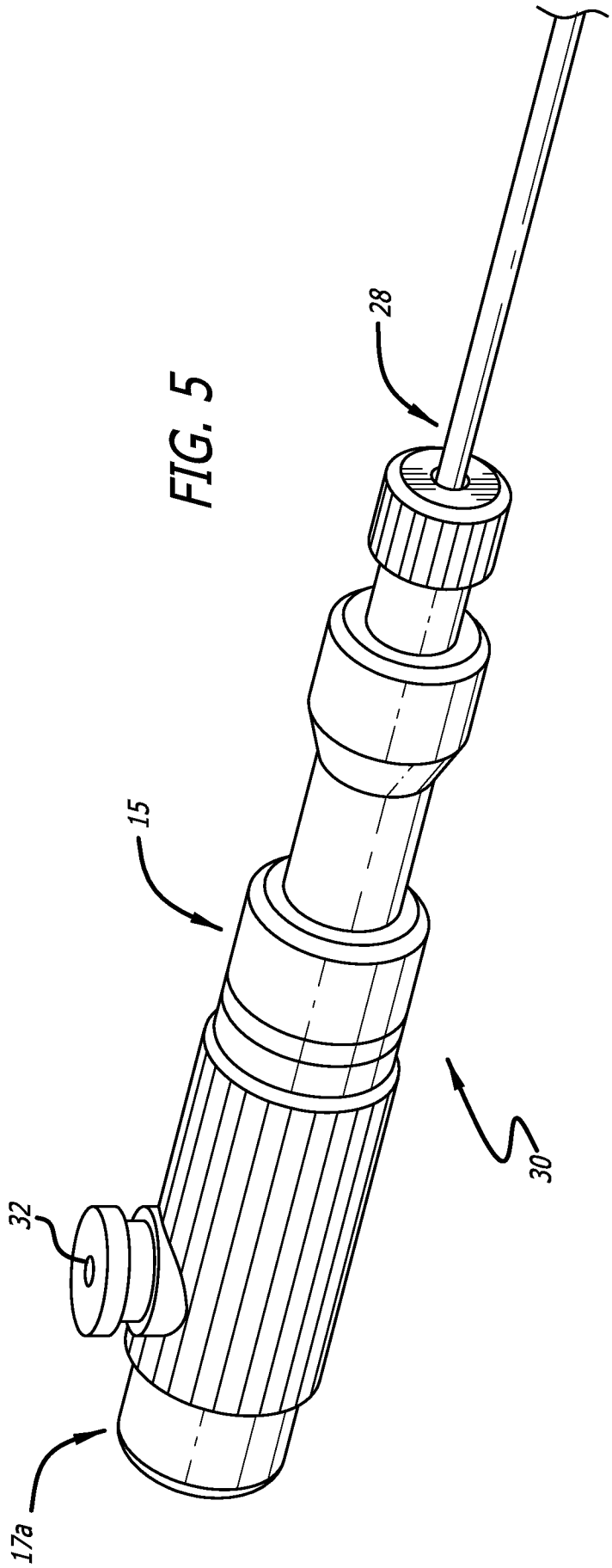


FIG. 6B

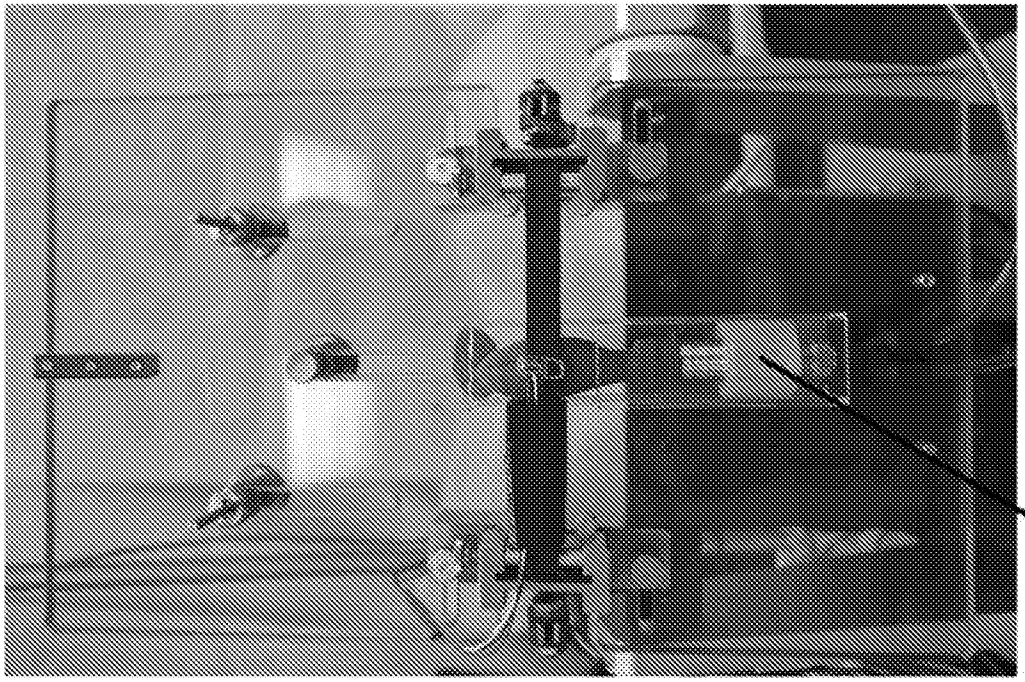
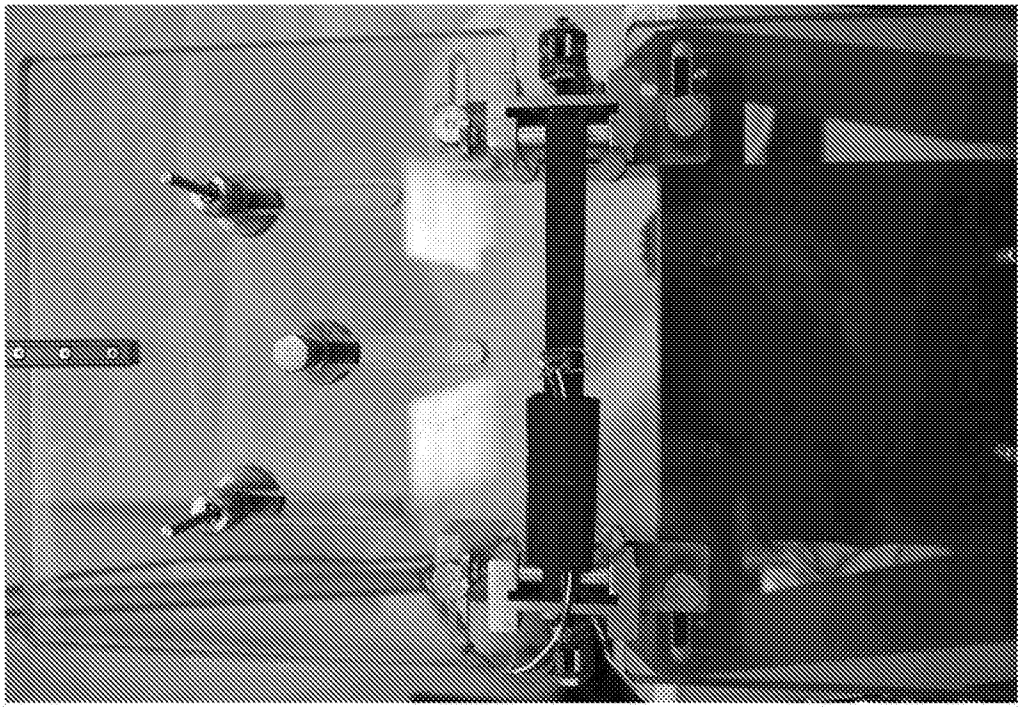


FIG. 6A



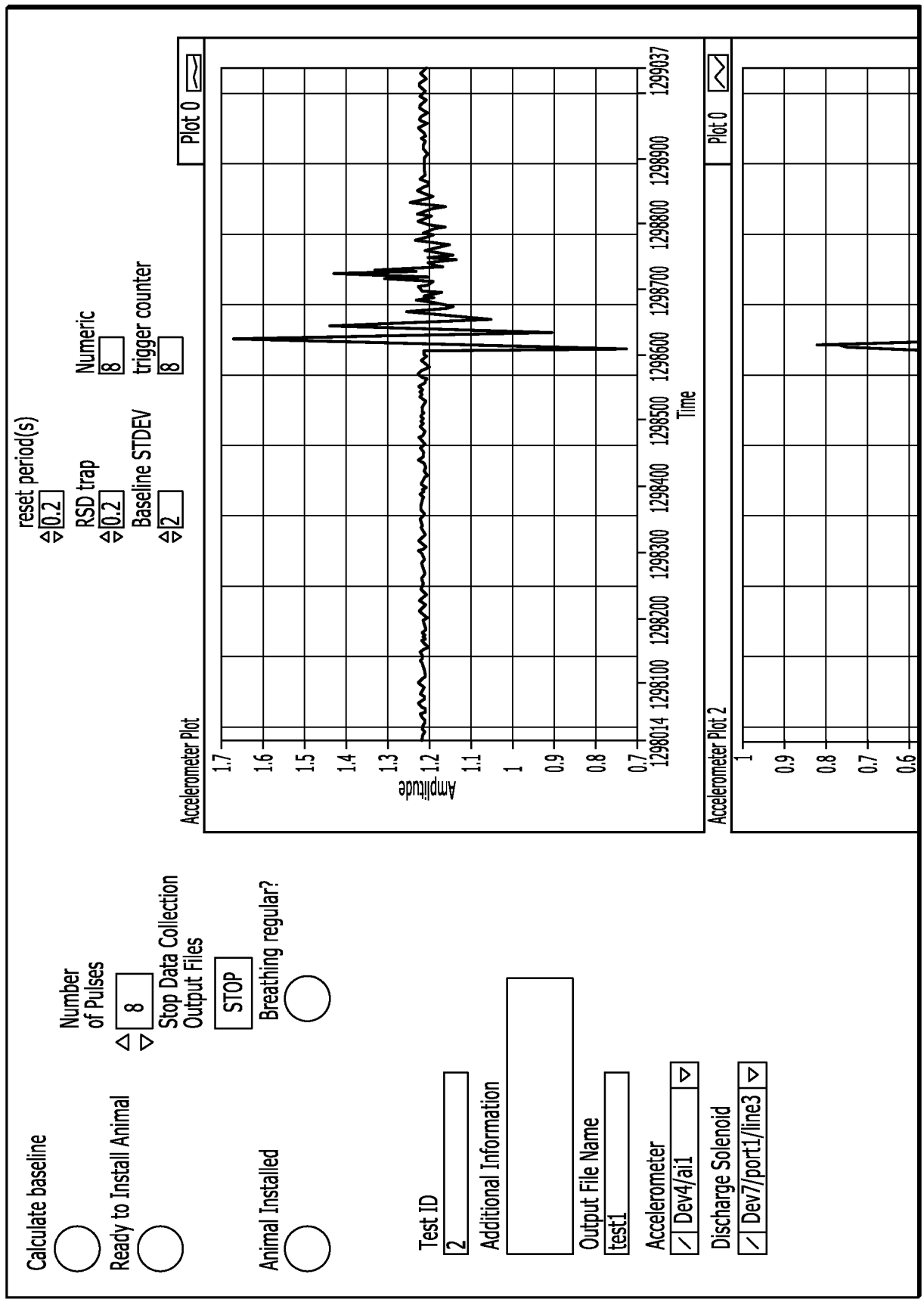

Calculate baseline
Ready to Install Animal
Number of Pulses
8
Stop Data Collection Output Files
STOP
Animal Installed
Breathing regular?
Test ID
2
Additional Information
Output File Name
test1
Accelerometer
Dev4/ai1
Discharge Solenoid
Dev7/port1/line3
reset period(s)
0.2
RSD trap
0.2
Baseline STDEV
2
Numeric
8
trigger counter
8
Plot 0
Accelerometer Plot
Amplitude
Time
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1
0.9
0.8
0.7
1298014
1298100
1298200
1298300
1298400
1298500
1298600
1298700
1298800
1298900
1299037
Accelerometer Plot 2
Plot 0
1
0.9
0.8
0.7
0.6

FIG. 7

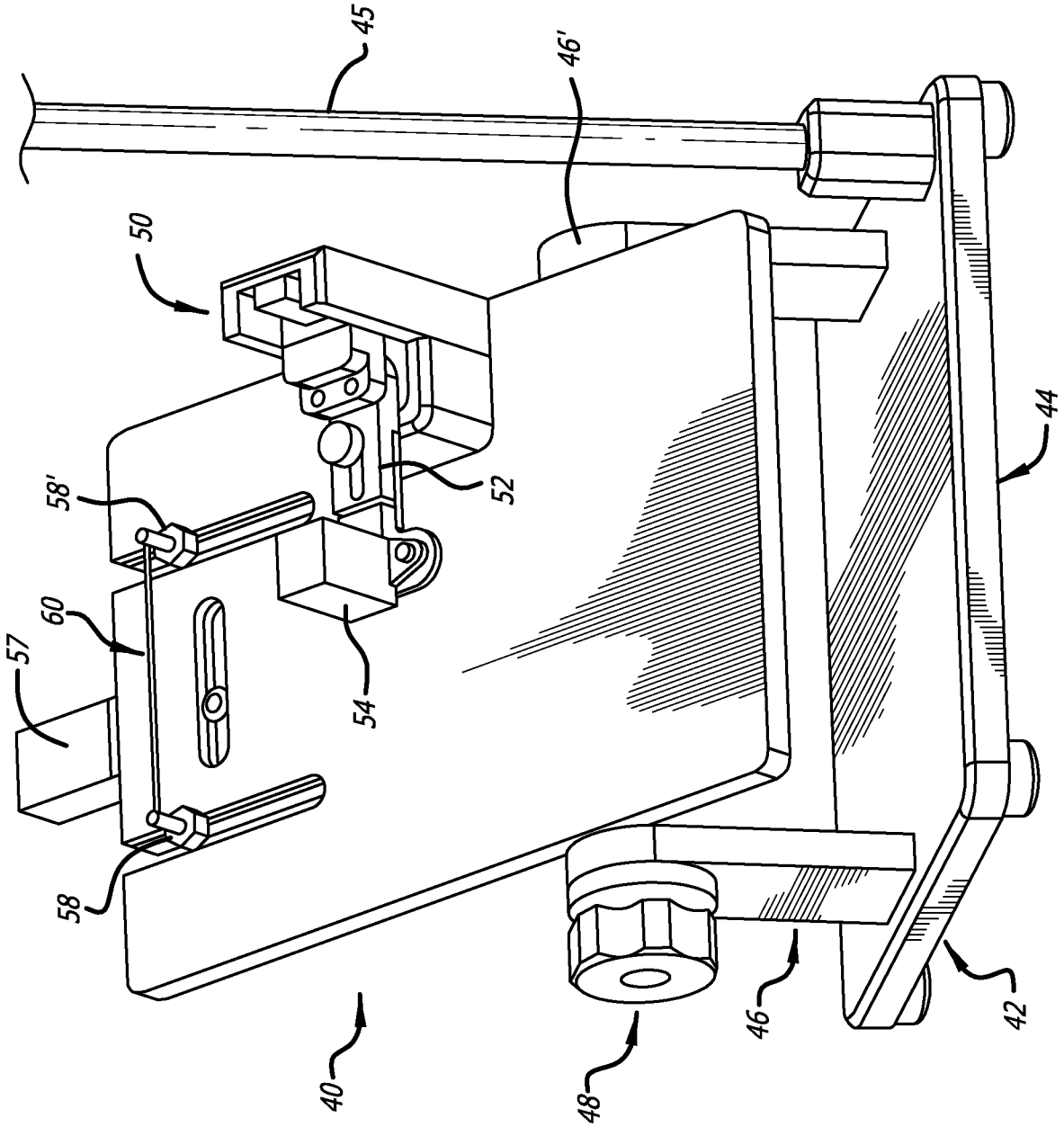
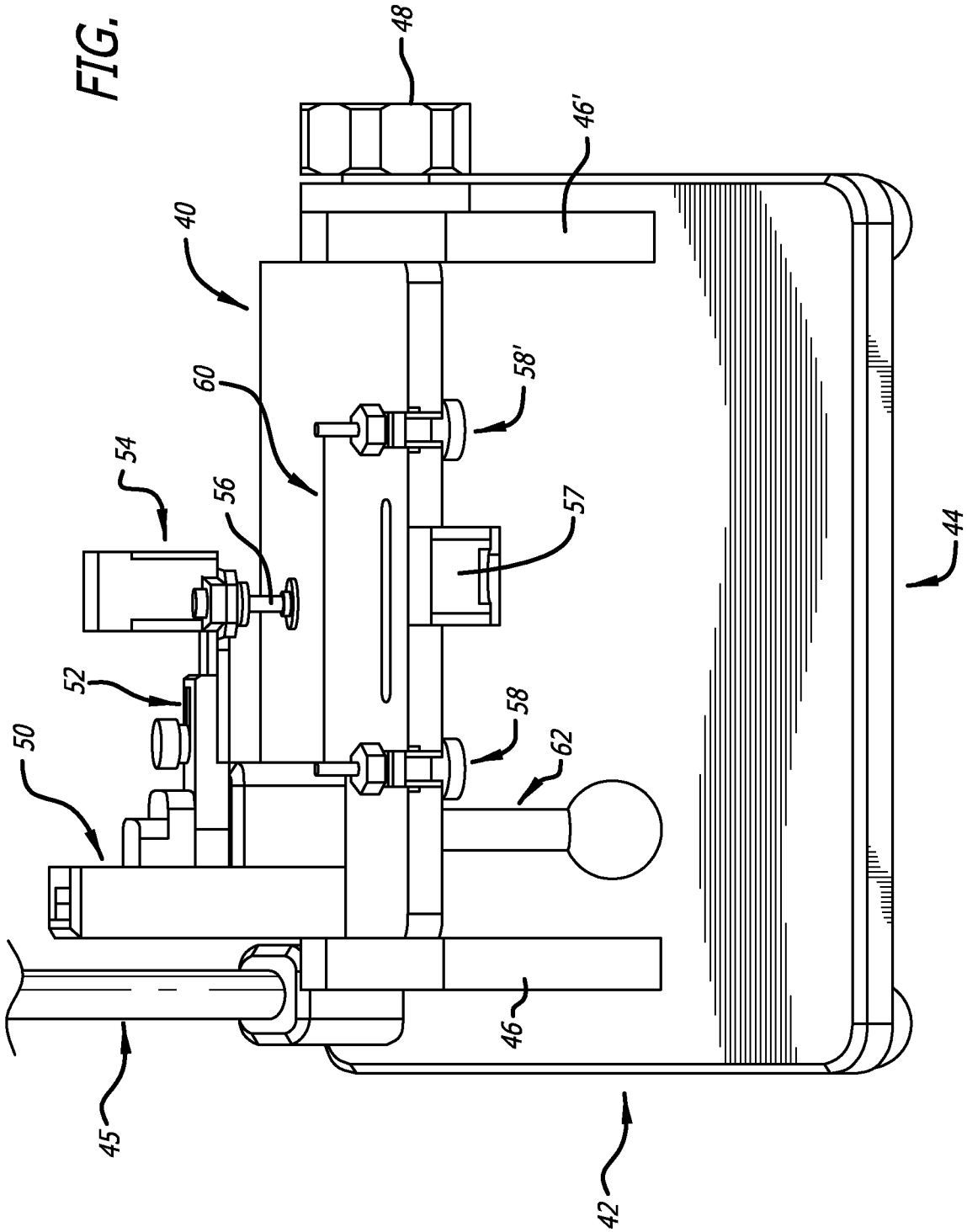


FIG. 8

FIG. 9



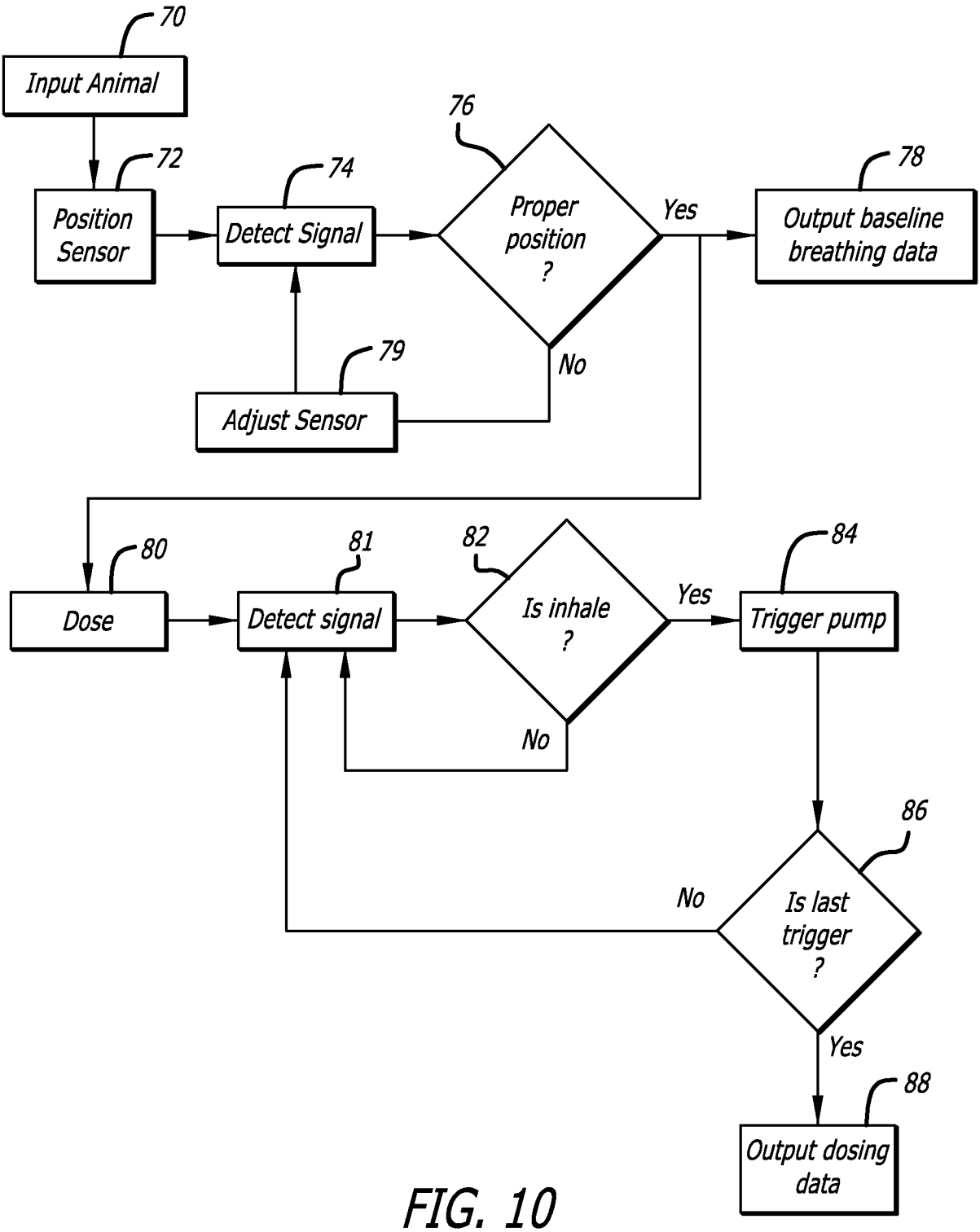

70
Input Animal
72
Position Sensor
74
Detect Signal
76
Proper position ?
Yes
78
Output baseline breathing data
No
79
Adjust Sensor
80
Dose
81
Detect signal
82
Is inhale ?
Yes
84
Trigger pump
No
86
Is last trigger ?
No
Yes
88
Output dosing data

FIG. 10

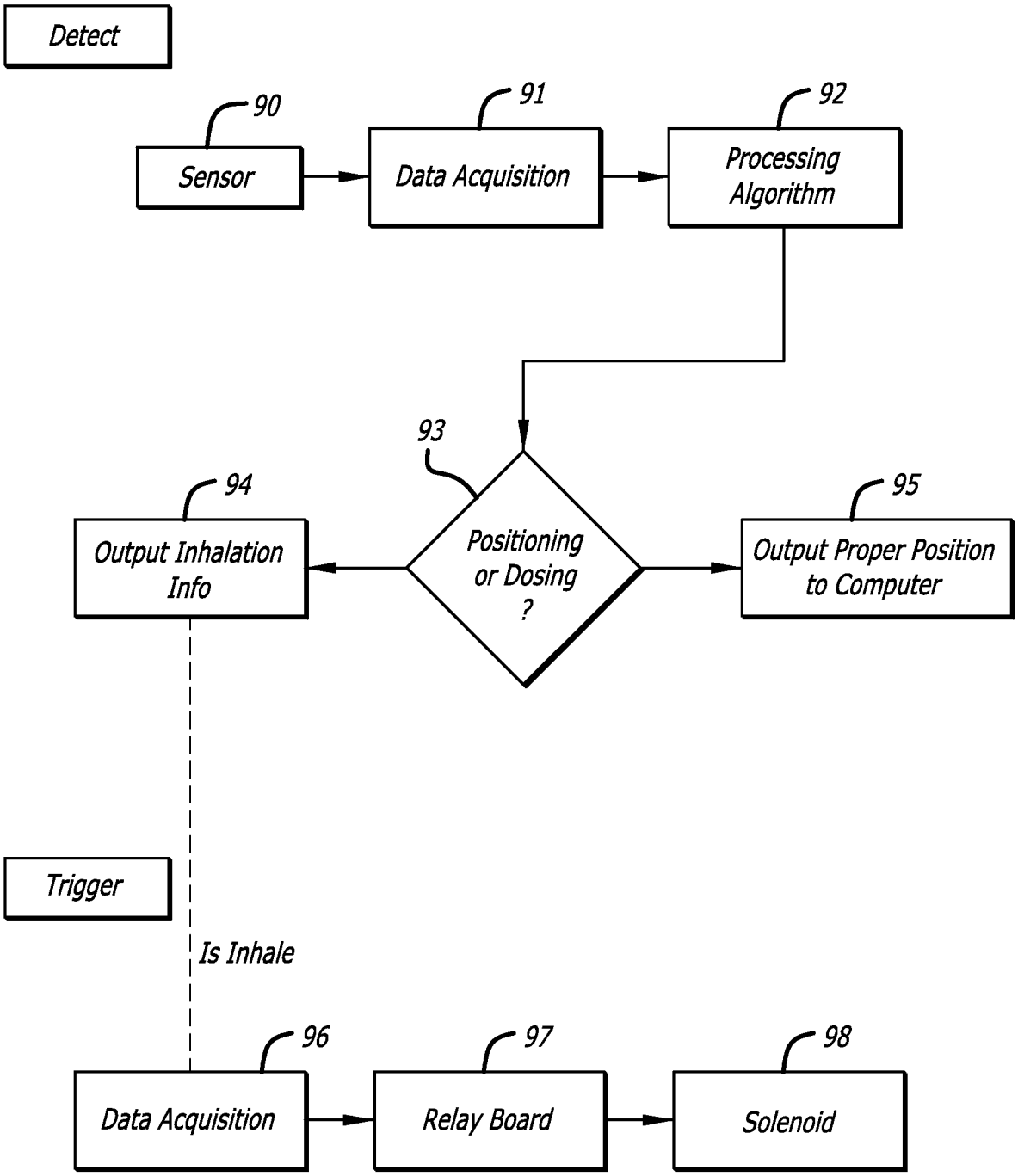

Detect
90
Sensor
91
Data Acquisition
92
Processing Algorithm
93
Positioning or Dosing ?
94
Output Inhalation Info
95
Output Proper Position to Computer
Trigger
Is Inhale
96
Data Acquisition
97
Relay Board
98
Solenoid

FIG. 11

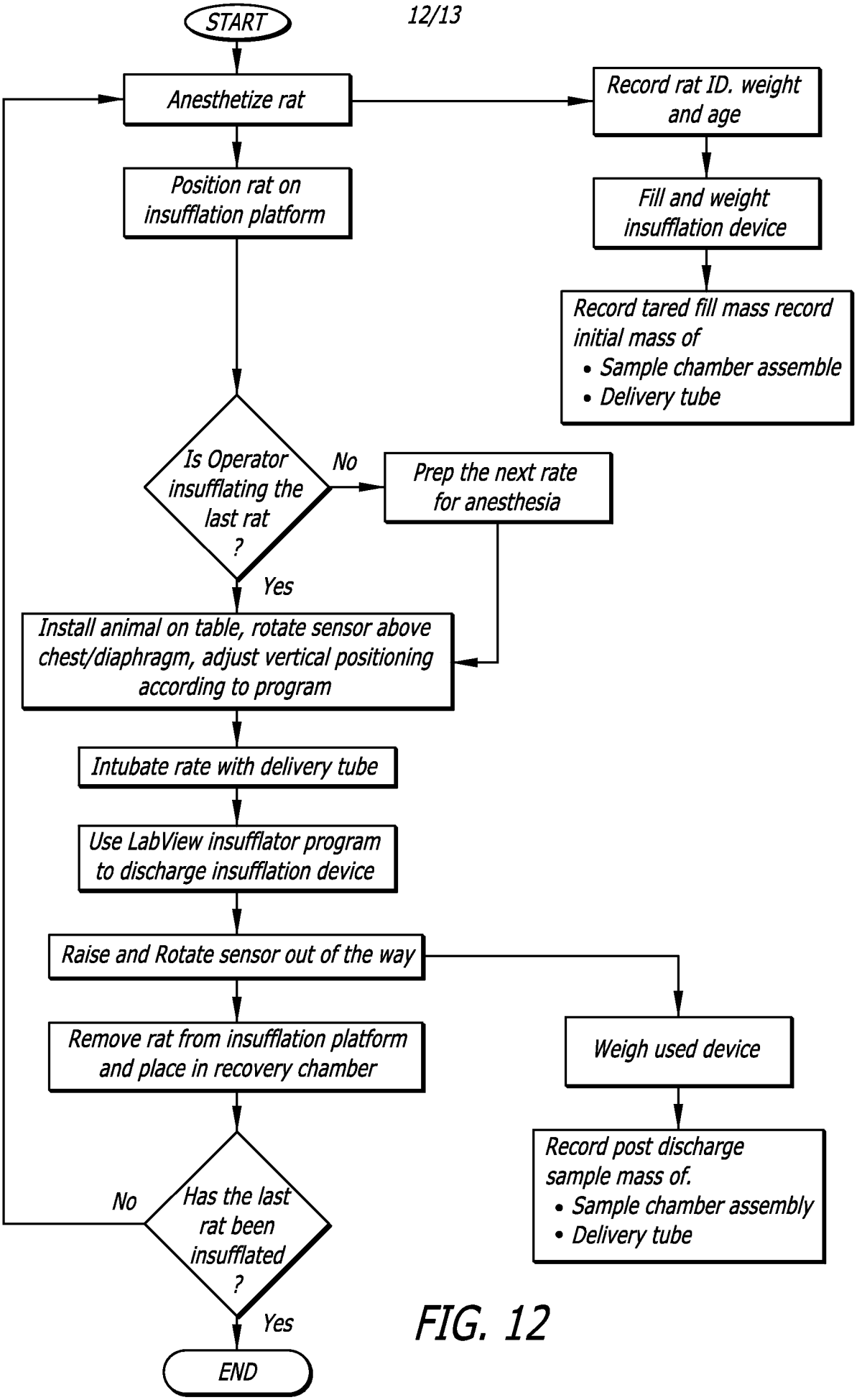

START
Anesthetize rat
Record rat ID. weight and age
Position rat on insufflation platform
Fill and weight insufflation device
Record tared fill mass record initial mass of
• Sample chamber assemble
• Delivery tube
Is Operator insufflating the last rat ?
No
Prep the next rate for anesthesia
Yes
Install animal on table, rotate sensor above chest/diaphragm, adjust vertical positioning according to program
Intubate rate with delivery tube
Use LabView insufflator program to discharge insufflation device
Raise and Rotate sensor out of the way
Remove rat from insufflation platform and place in recovery chamber
Weigh used device
Record post discharge sample mass of.
• Sample chamber assembly
• Delivery tube
Has the last rat been insufflated ?
No
Yes
END

FIG. 12

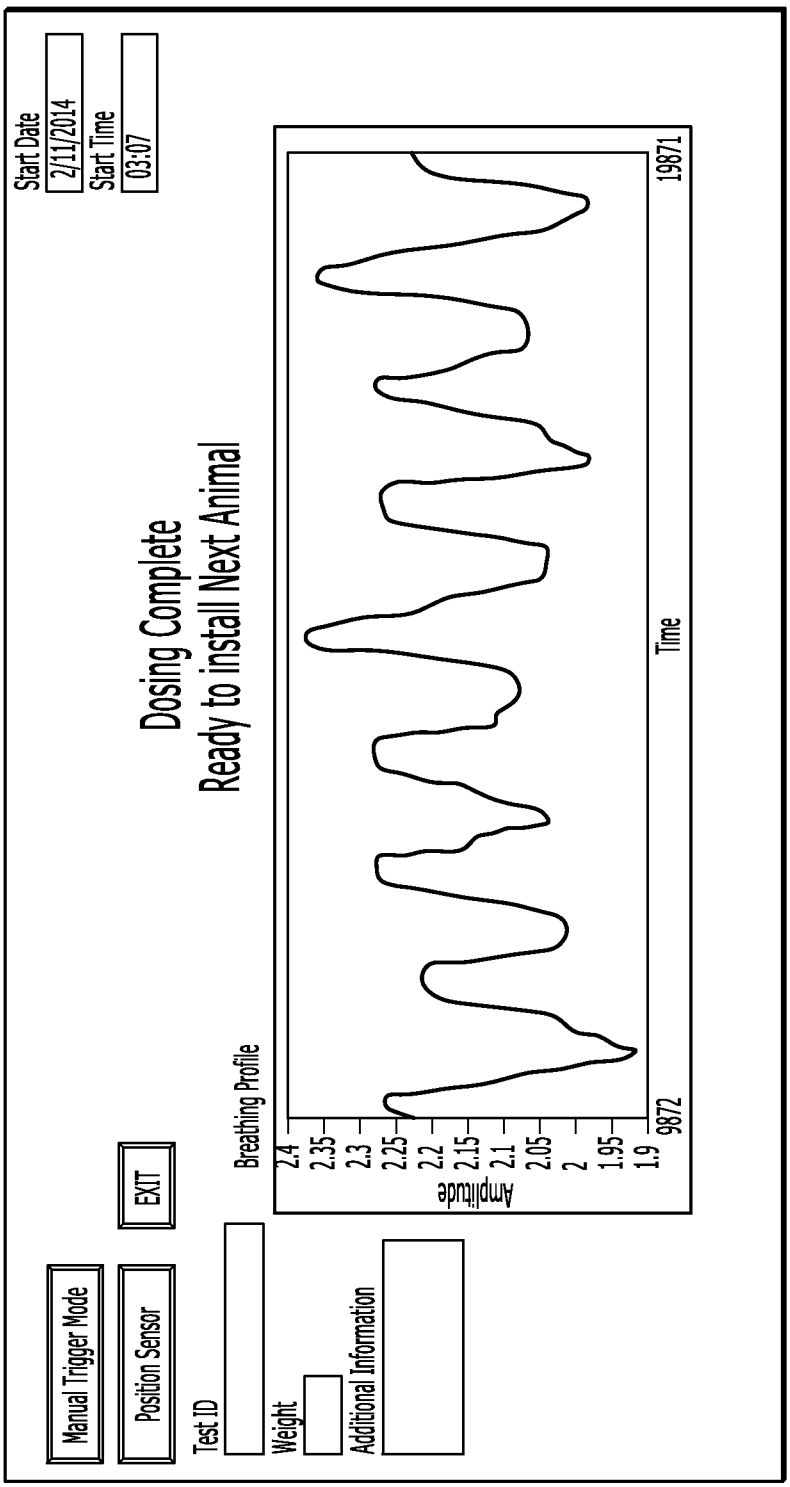

Start Date
2/11/2014
Start Time
03:07
Dosing Complete
Ready to install Next Animal
Manual Trigger Mode
Position Sensor
EXIT
Test ID
Weight
Additional Information
Breathing Profile
Amplitude
2.4
2.35
2.3
2.25
2.2
2.15
2.1
2.05
2
1.95
1.9
9872
19871
Time

FIG. 13

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/049817

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61M11/00 A61M15/00 A01K1/06
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61M A01K A61B

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US 2011/000482 A1 (GUMASTE ANAND [US] ET AL) 6 January 2011 (2011-01-06) abstract; figures 1, 2 paragraphs [0011], [0013] - [0016] -----	1-3,5-9 4,9
X A	US 2009/151720 A1 (INOUE MASAAKI [JP] ET AL) 18 June 2009 (2009-06-18) abstract; figures 1-7 paragraphs [0084], [0085], [0090], [0094], [0095], [0096], [0103], [0107] - [0109], [0113], [0130] - [0133] -----	1,2 3-9
Y	US 2004/163648 A1 (BURTON DAVID [AU]) 26 August 2004 (2004-08-26) abstract paragraph [0046] -----	4,9
	-/--	

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

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 November 2014	19/11/2014

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/049817

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2009/149727 A1 (TRUITT PATRICK [US] ET AL) 11 June 2009 (2009-06-11) the whole document	1-9
A	US 2008/015457 A1 (SILVA CARLOS D [AR]) 17 January 2008 (2008-01-17) the whole document	1-9
A	US 2008/255468 A1 (DERCHAK P ALEXANDER [US] ET AL) 16 October 2008 (2008-10-16) the whole document	1-9
A	US 6 279 511 B1 (LOUGHNANE MICHAEL H [US]) 28 August 2001 (2001-08-28) the whole document	1-9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/049817

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

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

1. [X] Claims Nos.: 10-18
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Claims Nos.: 10-18

Methods of providing ventilation to a subject as defined in claims 10-18 of the present application are methods for treatment of human or animal body by therapy. Indeed these methods are meant to provide an aerosolized powder plume to an animal during inhalation (see paragraph 0022). Thus, claims 10-18 relate to subject-matter considered by this Authority to be covered by the provisions of Rules 39.1(iv) and 67.1(iv) PCT, and no international search report has been established with respect to the subject-matter of these claims (Article 17(2)(a)(i)PCT). Consequently, no opinion will be formulated with respect to novelty, inventive step and industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i)PCT).

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2014/049817

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2011000482 A1	06-01-2011	CA 2766803 A1	06-01-2011
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US 2009149727 A1	11-06-2009	EP 2229094 A2	22-09-2010
		JP 2011505925 A	03-03-2011
		US 2009149727 A1	11-06-2009
		WO 2009076325 A2	18-06-2009
US 2008015457 A1	17-01-2008	NONE	
US 2008255468 A1	16-10-2008	EP 2214556 A2	11-08-2010
		US 2008255468 A1	16-10-2008
		WO 2009058866 A2	07-05-2009
US 6279511 B1	28-08-2001	NONE	