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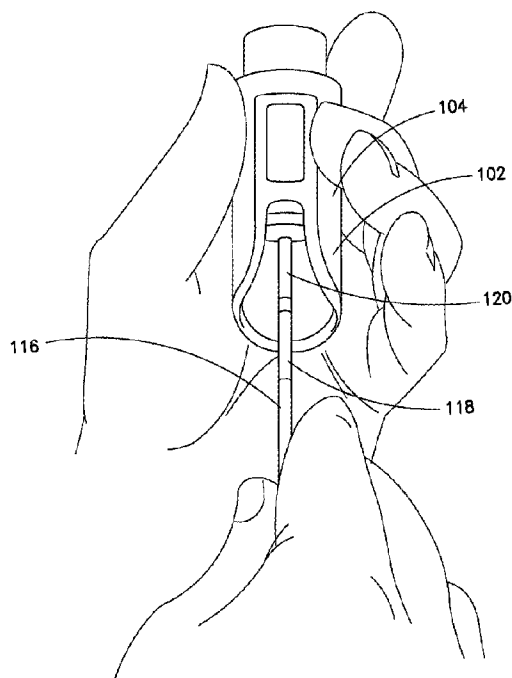
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(54) Titre : SYSTÈME ET PROCÉDE DE CAPTURE D'INFORMATIONS DE DOSE

(54) Title: SYSTEM AND METHOD FOR CAPTURING DOSE INFORMATION



(57) **Abrégé/Abstract:**

A system for capture of dose delivery information is provided. The system includes a medication delivery device, a dose information capture device adapted to be attached to the medication delivery device, and a target element adapted to be attached to the medication delivery device. The target element comprises a magnet or ferrous element and the target element attaches to the medication delivery device on a dose delivery mechanism of the medication delivery device. The dose information capture device includes a magnetic position sensor adapted to detect a position of the target element. As an alternative to magnetic sensing, MEMS flow sensors, and the like may also be used. Exemplary systems preferably transmit dose information in real time to remote devices for further processing.

Abstract

A system for capture of dose delivery information is provided. The system includes a medication delivery device, a dose information capture device adapted to be attached to the medication delivery device, and a target element adapted to be attached to the medication delivery device. The target element comprises a magnet or ferrous element and the target element attaches to the medication delivery device on a dose delivery mechanism of the medication delivery device. The dose information capture device includes a magnetic position sensor adapted to detect a position of the target element. As an alternative to magnetic sensing, MEMS flow sensors, and the like may also be used. Exemplary systems preferably transmit dose information in real time to remote devices for further processing.

SYSTEM AND METHOD FOR CAPTURING DOSE INFORMATION

FIELD OF THE INVENTION

[0001] The present invention relates to systems and methods for capturing the volume of medication delivered by a syringe or other medication delivery device.

[0002] In particular, the present invention relates to systems and methods for utilizing magnetic position sensing such as Hall-effect sensing and magnetoresistive (MR) sensing, Micro Electro Mechanical Systems (MEMS)

flow sensing, and the like in connection with various medication delivery devices and components to capture medication dose delivery information.

BACKGROUND OF THE INVENTION

[0003] Diabetes is a group of diseases marked by high levels of blood glucose resulting from defects in insulin production, insulin action, or both. There are 25.8 million people in the United States, or 8.3% of the population, who have diabetes. The total prevalence of diabetes has increased 13.5% since the 2005-2007 time period. Diabetes can lead to serious complications and premature death, but there are well-known products available for people with diabetes to help control the disease and lower the risk of complications. Chronic hyperglycemia leads to serious sometimes irreversible complications including renal failure, peripheral neuropathy, retinopathy, and vascular system complications.

[0004] Treatment options for people with diabetes include specialized diets, oral medications and/or insulin therapy. The primary goal for diabetes treatment is to control the patient's blood glucose (sugar) level in order to increase the chances of a complication-free life.

[0005] Idealized diabetes therapy would include continuous monitoring of blood glucose levels, data capture for insulin dosing, dietary intake, such as carbohydrate estimation, activity tracking, stress levels, and other factors. By continuously monitoring, healthcare professionals can maximize the effectiveness of the treatment regimen for each patient. Unfortunately, conventional diabetes treatments, including multiple daily injections (MDI), insulin pens, patch pumps and insulin pumps, do not adequately record information on medication doses delivered to the patient to provide feedback to the doctor. Accordingly, the conventional feedback loop between doctors and patients is less frequent, and based mainly on qualitative assessments between the doctor and patient. Accordingly, there is a need to enhance medication delivery

devices and methods to add informatics such as dose delivery capture, to provide enhanced feedback to healthcare professionals to improve diabetes therapy.

[0006] In order to properly diagnose and treat diabetes mellitus (DM) the patient and/or Health Care Provider (HCP) needs to evaluate the short-term, daily records for (1) insulin dosing, (2) oral medications, (3) Blood Glucose Measurement (BGM), and (4) carbohydrate intake. These data are obtained from different sources, such as the setting on an insulin pen, the episodic reading from a BGM meter, and the estimate of carbohydrates in a meal all determined and transposed by the patient into a logbook or diary. This method of recording data is extremely tedious and prone to errors and omissions. Even in the best case scenario, when the historical records are complete, the insight that can be obtained is limited without transposing the hand written data to software that can reconfigure the data to evaluate trends and support therapeutic modifications. As a result the majority of patients do not properly maintain their logbook, which reduces the ability of the patient and the doctor to properly diagnose the disease, which can ultimately result in poor adherence to therapy and poor glycemic control. Accordingly, a system is required to automatically capture, store, transfer, and enable optimal assessment of all the data necessary for the proper diagnosis and treatment of Diabetes Mellitus.

[0007] U.S. Patent No. 8,613,719 describes a monitor that can be attached to the patch pen, which can sense and wirelessly transmit the time of each delivery event. A flag, such as a magnet, is placed on the movable linkage within the patch pen, and a sensor within the monitor attachment detects the proximity of the magnet at the end of the linkage travel, that is, at the end of the delivery cycle.

SUMMARY OF THE INVENTION

[0008] The above described disadvantages are overcome or minimized and the above and other advantages are realized by embodiments of the present invention. Exemplary embodiments of the present invention provide a device for capturing delivered dose information. The device includes a medication delivery device, a dose information capture device adapted to be attached to the medication delivery device, and a sensor element adapted to be attached to the medication delivery device. The sensor element preferably comprises at least one of either a magnet, preferably a permanent magnet, although a non-permanent magnet could be used, and at least one a ferrous element, and attaches to the medication delivery device on a dose delivery mechanism of the medication delivery device. The dose information capture device includes a magnetic position sensor adapted to detect a position of the sensor element.

[0009] Accordingly, embodiments of the present invention provide a device that senses a delivered dose by magnetic position sensing. Magnetic position sensing is accomplished by Hall-effect sensors, magnetoresistive sensors, or any other suitable device. Various embodiments may sense linear translation, rotational movement, flow, or medication level within an insulin vial or reservoir. Magnetic position sensing determines linear or rotational movement of the mechanical linkage or mechanization that correlates with the dose to be delivered in an insulin pen or other drug delivery device, as will be described herein. In other embodiments magnetic position sensing is utilized to determine the level of fluid in a vessel, such as by linear translation or change in position of a magnet floating on a top surface of insulin. Flow sensing, particularly MEMS flow sensors, include coriolis, capacitance, and thermal sensors such as Time of Flight (ToF) sensors used to determine the volume of drug delivered from a pen, syringe or other drug

delivery device. Capacitance sensing is preferably used to measure and determine the level of liquid, such as insulin, in a vessel such as an insulin vial.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] The above and other exemplary features and advantages of certain exemplary embodiments of the present invention will become more apparent from the following description of certain exemplary embodiments thereof when taken in conjunction with the accompanying drawings, in which:

[0011] FIG. 1 illustrates an informatically enabled vial sleeve according to an exemplary embodiment of the present invention;

[0012] FIG. 2A illustrates flux density over distance in a Hall-effect sensor and magnet arrangement utilized with an exemplary embodiment of the present invention;

[0013] FIG. 2B illustrates a substantially linear output voltage over flux density curve for a Hall-effect sensor arrangement utilized with an exemplary embodiment of the present invention;

[0014] FIG. 3 illustrates an informatically enabled vial sleeve according to an exemplary embodiment of the present invention;

[0015] FIG. 4 illustrates an informatically enabled vial sleeve according to another exemplary embodiment of the present invention;

[0016] FIG. 5 illustrates a pen cap and flow sensor according to an exemplary embodiment of the present invention;

[0017] FIG. 6 illustrates an informatically enabled attachment for a reusable or disposable pen according to an exemplary embodiment of the present invention;

[0018] FIG. 7 illustrates a multi-pole magnetic ring and Hall-effect sensor arrangement for use with the attachment illustrated in FIG. 6;

[0019] FIG. 8 illustrates a fixed dose pen according to an exemplary embodiment of the invention;

[0020] FIG. 9 is another illustration of either an adjustable or fixed dose pen;

[0021] FIGS 10 and 11 illustrate embodiments of informatically enabled mechanical patch pens according to exemplary embodiments of the invention;

[0022] FIG. 12 illustrates an informatically enabled pen case according to an exemplary embodiment of the present invention;

[0023] FIG. 13 illustrates an informatically enabled pen case according to another exemplary embodiment of the present invention;

[0024] FIG. 14 illustrates an informatically enabled syringe sleeve according to another exemplary embodiment of the present invention;

[0025] FIG. 15 illustrates an informatically enabled vial sleeve utilizing capacitance sensing according to another exemplary embodiment of the present invention;

[0026] FIG. 16 illustrates an informatically enabled vial sleeve, according to another exemplary embodiment of the present invention;

[0027] FIG. 17 illustrates another informatically enabled vial sleeve, according to another exemplary embodiment of the present invention;

[0028] FIG. 18A and 18B illustrate a linear magnetic position sensing arrangement attached externally to a syringe according to an exemplary embodiment of the invention;

[0029] FIG. 19A-19D illustrate an informatically enabled injection port;

[0030] FIG. 20 illustrates a wireless communication system including an informatically enabled medicine delivery device according to an exemplary embodiment of the present invention;

[0031] FIG. 21 illustrates a system for identifying pen needles according to an exemplary embodiment of the invention;

[0032] FIG. 22 illustrates another system for identifying pen needles according to an exemplary embodiment of the invention;

[0033] FIG. 23 illustrates another system for identifying pen needles according to an exemplary embodiment of the invention; and

[0034] FIG. 24 illustrates yet another system for identifying pen needles according to an exemplary embodiment of the invention;

[0035] FIG. 25 illustrates a combination hall effect sensor and ring magnet according to an exemplary embodiment of the invention;

[0036] FIG. 26 illustrates a rotary device adapted to work with an insulin pen according to an exemplary embodiment of the invention;

[0037] FIG. 27 illustrates the hand hold configuration of an embodiment of the invention;

[0038] FIG. 28 illustrates a linear dose measurement apparatus according to an exemplary embodiment of the invention;

[0039] FIG. 29 illustrates a thermal time of flight sensor embodiment of the present invention;

[0040] FIG. 30 illustrates the embodiment of FIG. 29 with a cap removed;

[0041] FIG. 31 illustrates the embodiment of FIG 29 with a cap installed;

[0042] FIG. 32 is an exploded view of a thermal time of flight dose measurement system according to an exemplary embodiment of the invention;

[0043] FIG. 33 is a first view of a disposable portion of the embodiment shown in FIG. 32;

[0044] FIG. 34 is a second view of the disposable portion of FIG. 33;

[0045] FIG. 35 is a cross-sectional view of the disposable portion of FIGS. 33-34;

[0046] FIG. 36 is an exploded view of a durable portion of an exemplary embodiment of the invention;

[0047] FIG. 37 illustrates a thermal time of flight sensor according to an exemplary embodiment of the invention;

[0048] FIGS. 38-40 illustrate interactions between the disposable portion, the durable portion, the insulin pen, and the pen needle according to an exemplary embodiment of the invention;

[0049] FIG. 41 illustrates a close up of the z-axis film according to an exemplary embodiment of the invention;

[0050] FIG. 42 is a close up view further illustrating operation of a thermal time of flight sensor according to an exemplary embodiment of the invention;

[0051] Throughout the figures, like reference numbers will be understood to refer to like elements, features and structures.

DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS

[0052] In the example provided below, insulin delivery is described. However, it should be understood that insulin delivery is merely exemplary, and any medicament delivery is contemplated to be within the scope of the invention. Informatics is defined herein as an interdisciplinary field primarily concerned with the analysis, collection, classification, manipulation, storage, retrieval, movement, and dissemination of information.

[0053] Exemplary embodiments of the present invention capture the amount or volume of medicament being delivered by either a syringe, insulin pen, or other drug delivery device. Several primary fields of technology, magnetic position sensing including Hall-effect sensing, magnetoresistive (MR) sensing, including anisotropic MR, MEMS flow sensing including thermal time of flight (ToF) sensing, micro-Coriolis and capacitive pressure sensing, are applied

to various devices and device components to enable dose capture. MEMS capacitive pressure sensing uses Bernoulli's principle and/or the empirical Darcy-Weisbach equation are utilized to detect a change in pressure by changing the diameter of the conduit in the flow sensing element, and the pressure is measured using two capacitive MEMS pressure sensors located respectively in sections of conduit having different diameters. In the exemplary embodiments described herein, it should be understood that any type of MEMS flow sensing may be utilized in place of magnetic position sensing. It should be understood that embodiments of the present invention are not limited to Hall-effect sensing and MEMS flow sensing, but rather any suitable sensing technology is within the scope of the present invention.

[0054] Conventional Hall sensors are sensitive only to magnetic fields that are perpendicular to the chip surface, that is, one dimensional or 1D. 3D Hall sensors advantageously also respond to magnetic fields parallel to the chip surface. The sensor chip has a separate sensor for each of the three magnetic axes, and converts the magnetic field data into absolute position information using a simple two pole magnet as the magnetic field source. For a linear sensing application, the 3D Hall sensor would be used in 2D mode. One advantage of this system for linear sensing is that it allows for larger separation between magnet source and sensor than standard 1D Hall sensors.

[0055] A basic Anisotropic Magnetoresistive (AMR) sensor uses a single saturated-mode Wheatstone bridge, typically made from Permalloy (Ni-Fe alloy), that creates an output voltage with respect to the direction of the magnetic flux passing over the sensor surface. Thus it operates in saturation mode to avoid interference from stray magnetic fields and the magnetic field that it senses is across the face of the chip, contrasting with the perpendicular field of a Hall sensor. The AMR sensor creates an analog output voltage that varies with the direction of the

magnetic flux passing over the chip surface. The minimum field required to put the AMR sensor into saturation mode is typically 50-80 gauss. A single element AMR sensor has a $\pm 45^\circ$ range of operation where voltage-to-angle output is linear.

[0056] Embodiments of the present invention preferably meet the following functional capabilities. First, embodiments of the present invention preferably electronically capture the amount of pharmaceutical injected and the time of the injection event. Second, they preferably provide a means of associating the captured injection event data with the type of pharmaceutical injected. Drug identification technology may be incorporated into embodiments of the present invention, and are described in U.S. Published Application Nos. 2012/0222468, 2012/0226447, and 2012/0226446 .

Third, they are preferably compatible with existing, commonly prescribed diabetes pharmaceutical pens and other devices utilized for MDI or infusion therapy. Fourth, they transmit captured data in a common digital format compatible with smart phones or similar devices to be utilized in patient software such as a patient meaning engine. A patient meaning engine receives data, including any combination of, but not limited to the following: patient blood glucose levels, calorie intake, exercise, medication doses, and other relevant data. One function of the engine is to track trends in the data and provide feedback to a user to enhance the effectiveness of patient self-care through improved understanding of the patient's disease and therapy in the patient's daily life. The meaning engine provides feedback to the patient to promote self-therapy and enables improved decision making during dosing events, e.g. prandial dosing. This feedback and the additional insight afforded by the meaning engine provide sufficient value to the patient during dosing events to influence behavioral modification. The meaning engine can also provide information or alerts to healthcare providers so that deviations

from healthy trends are identified and proactively acted upon. The use of a meaning engine as defined herein promotes efficient use of physician time and eliminates or reduces poor medical treatment regimens that rely on fail-first as opposed to identifying the shortest path to a cost effective outcome. Fifth, they preferably transmit captured data to the patient meaning engine within one minute of sensing the delivered dose. Sixth, they capture data from all prescribed forms of T1 and T2 insulin and oral dose regimens. Seventh, their accuracy preferably satisfies injection standard ISO 11608. One example of utilizing the meaning engine would be titrating a new drug for a patient. Patients using a new drug, such as slow acting insulin, for the first time, by adjusting the dose weekly, every few days, or as required based on analyzing insulin doses delivered and blood glucose readings over a period of time. The adjustments and data could be sent to the patient's doctor to close the loop between the doctor and patient daily, or as necessary, while saving time for the doctor and expediting the titration process for the patient. Of course insulin is used herein as an example, and any suitable drug could similarly be titrated by monitoring relevant factors such as medicine doses and blood glucose levels or the like.

[0057] Embodiments of the present invention further preferably meet the following additional criteria. They can be carried with the patient and used anytime, anywhere. They preferably do not increase the number of items a diabetes patient normally carries. They are compatible with other elements in an informatics enabled outcome (IEO) system, such as Blood Glucose Monitors (BGM) and oral medicine adherence devices; that is, data transfer between devices in the system utilize a common communication platform.

[0058] Embodiments of the present invention are preferably easy for the patient to use; that is, the device or system functionality preferably does not require a high level of user expertise or

significant training. Embodiments of the present invention improve patient safety, and preferably do not compromise patient safety in any way.

[0059] Exemplary embodiments of the present invention informatically enable medicament delivery devices to affirmatively capture dose delivery information. The following devices and device components typically associated with dose delivery are appropriate for informatics enablement. A vial or drug reservoir attachment can sense movement of a syringe plunger. A vial or drug reservoir attachment can also sense the level of drug within a vial or reservoir to determine the volume remaining and hence the dose delivered. A pen cap can sense movement of the plunger in an insulin pen by magnetic sensing means. A magnetic sensor is preferably incorporated into a disposable insulin pen to determine plunger position. A sleeve with an integral flow sensor can be placed between an insulin pen and a pen needle. A cartridge for a reusable pen can include a sensor to determine plunger position in the cartridge. A cartridge filler can be utilized to attach a sensing element to a cartridge. A mechanism attached to the end of an insulin pen that exchanges a cannula into and from a reusable cannula hub can be provided with a flow sensor. A pen case may be provided with a magnetic position sensor to determine the position of a plunger within an insulin pen when returned to its pen case. A patch pump configured to deliver a preset number of insulin units per activation (button press) can be configured with a sensor to sense button presses. An injection patch, similar to the Insuline “Insupad” can be modified to channel the flow from different injections through a flow sensor. An injection port, similar to the device provided by Patton Medical, can also be modified in the same manner. An insulin vial or fluid reservoir can be modified to incorporate an internal floating magnet and an external sleeve with integrated magnetic sensors. Any all-in-one type device can be provided with appropriate sensors as described herein to capture dose information.

As used herein, an “All-In-One” device should be understood to be a combination device, such as a device which includes for example a BGM and a method to deliver insulin dosing or a BGM and a bolus calculator. An attachment for a syringe in which at least one sensor element is connected to the syringe plunger and at least one sensor is attached to the syringe barrel.

[0060] A first embodiment of the invention is shown in FIG. 1 which shows an attachment 102 for an insulin vial and a modified insulin syringe. A reusable attachment 102 engages with an insulin vial, and preferably remains attached until the insulin is exhausted. The vial attachment 102 includes at least one linear Hall-effect sensor 104 with an analog output, a flexible Printed Circuit Board Assembly (PCBA) 106, a battery 108, a power management system 110, a Bluetooth Low Energy (BLE) wireless transceiver 112, and a Real Time Clock (RTC) 114. During the manufacturing process for the syringe 116, an RFID chip 118 is placed into the syringe 116, and a permanent magnet 120 is over-molded into the stopper or plunger. In an alternate embodiment a ferrous target, such as a steel disc or slug, is used rather than a magnet to further reduce the cost of the disposable significantly.

[0061] When a ferrous target is utilized, the Hall-effect sensor 104 is preferably back biased by integrating a magnet with the Hall sensor 104, so that a ferrous object in range will be sensed by the Hall sensor 104.

[0062] The vial attachment 102 reads the RFID chip in the syringe 116 to determine the inner diameter (ID) of the syringe barrel. The Hall-effect sensor 104 measures the linear movement of the plunger, and the dose is calculated from the ID and the plunger travel. The dose amount is time stamped and wirelessly transferred to a smart phone and/or to the “cloud” or internet. Alternately, a phone application (APP) for a Smart phone is provided in which the phone camera captures an image of the syringe just prior to injection. The syringe diameter would be

recognized either by a bar code, a QR code, or the like printed on the outside of the syringe barrel, or a comparative measurement, or other optical methods that are part of a Smart phone, and the distance between the plunger and the nozzle, just prior to injection, could be determined by the same method. Similarly to the previous embodiment, these two values are then used to calculate the dose. The numerous features described herein can also be combined to provide additional embodiments, e.g. the Smart phone APP could replace the need for the RFID chip, in combination with a vial attachment that measures the movement of the plunger by sensing the position of the embedded magnet.

[0063] FIG. 2A illustrates a flux density curve sensed by a Hall-effect sensor described above as a magnet passes the sensor in close proximity. FIG. 2B illustrates the substantially linear analog output voltage response of a Hall-effect sensor used in embodiments of the present invention. Hall-effect sensors preferably convert the linear output voltage to a digital signal for output to a processor, or the like, for further processing.

[0064] FIG. 3 is a cross sectional view of a syringe and vial with an informatically enabled vial attachment according to an exemplary embodiment of the invention. Depending on the total stroke intended to be sensed, multiple Hall-effect sensors may be used, but for a short stroke, only one Hall-effect sensor is needed.

[0065] A second embodiment of the invention is shown in FIG. 4. A magnetic strip 202 is over-molded into the syringe plunger. The strip 202 has numerous magnetic poles 204 that repeatedly alternate from north to south over the length of the strip. As in the first embodiment, a vial attachment would include the componentry necessary to read the RFID chip, sense the position of the plunger, and wirelessly communicate the volume of insulin injected. In this embodiment, high resolution (positional accuracy) is achieved using the same basic principle as used in an

optical encoder. That is, a stacked set of magnets form a series of north and south magnetic poles that are sensed in a similar manner to black and white (or opaque and optically transmissive) optical patterns on an optical encoder. The position sensor can be a single integrated circuit that incorporates multiple Hall-effect sensors, which are arranged to detect the motion of the magnetic strip with high-resolution output that can be interfaced directly to a microcontroller. Such high resolution magnetic position sensors are available from, for example, Austria Micro Systems, ams AG. In combination with a multipole strip, a single high resolution magnetic position sensor can sense pole pairs passing the face of the sensor in order to accommodate any length stroke with a single sensor. High resolution single-chip sensors with multiple Hall-effect sensors are advantageously compact and can be used for both linear and off-axis rotary motion sensing. These devices offer resolutions down to 15 microns (μm). As a reference, for a 1 ml syringe with 0.478 cm internal diameter, 56 μm displacement of the plunger would equate to 0.1 units or 0.001 ml.

[0066] A third embodiment of the invention is shown in FIG. 5, which illustrates a disposable or reusable insulin injection pen 500. Any suitable flow sensor, including preferably Micro-Electro-Mechanical Systems (MEMS) flow sensors could be utilized to provide an informatically enabled insulin pen. One type is a MEMS micro-Coriolis mass flow meter which utilizes an oscillating tube to precisely measure the force of mass flow within the tube. A second type is a thermal sensor, such as a MEMS thermal time-of-flight flow sensor. In addition, a pair of MEMS capacitive pressure sensors on either side of a restriction can be used. A pen attachment 502 comprises a reusable 504 and disposable 506 portion. The reusable portion 504 is a pen cap or sleeve that attaches to the delivery end of insulin pen and is used until the insulin in the pen is exhausted. The disposable portion 506 is a plastic molded component in the shape of a small

cylinder and has a MEMS flow sensor integrated into a fluidic channel through which the insulin flows. The disposable MEMS cylinder is attached to the end of the pen, and the pen needle is attached to the MEMS cylinder. A removable or retractable end cap is used to protect and expose the MEMS cylinder and allows the patient to exchange the pen needle at the time of use. The dose is preferably captured at the precise time of delivery, data is time stamped, and wirelessly transferred to a smart phone and/or the “cloud” or internet.

[0067] MEMS sensors typically come prepackaged by a manufacturer. Conventional MEMS sensors as described above contain not only the specific MEMS component which is necessarily very small, but also related electronics and circuitry. However, in embodiments of the present invention, the small MEMS component is preferably separated from the related circuitry. In this manner, the small MEMS component may be disposable, and the related circuitry can be reusable. In the embodiment shown in FIG. 5, for example, the small MEMS component would be located in the disposable flow sensor 506, while the related circuitry would be located in the reusable pen cap 504. This arrangement has significant cost advantages for manufacturing. As an example, a conventional MEMS sensor package may cost ~\$10, while the small MEMS component may cost less than ~\$1. Accordingly, it is advantageous to separate the small MEMS component from the related circuitry so that the expensive portion may be reused, and the less expensive portion may be disposable. Alternately a magnet is attached or incorporated into the plunger of an insulin cartridge adapted for insertion into an insulin pen. In one exemplary embodiment a Hall-effect sensor is incorporated into a pen cap, and detects the position of the plunger after injection when the pen cap is placed back on the pen. The relative movement of the cartridge plunger before and after injection corresponds to the dose amount, which is recorded, logged and preferably transmitted to a remote device such as cloud-based storage for further

processing and feedback. In another exemplary embodiment, the Hall-effect sensor and related circuitry are located in the pen case, and the relative movement of the cartridge plunger is measured each time the insulin pen is placed back into the pen case. This embodiment has the advantage of using the large amount of space available in the pen case for the Hall-effect sensor and related electronics. Cartridge plunger position in a pen case can be measured utilizing, for example, the AMS5410 3D Hall sensor. Multiple sensors can be used to triangulate accurate displacement of the cartridge plunger with reference to the pen injector or cartridge, with a 40mm per sensor range.

[0068] To enable the systems described herein to capture dose delivery in real time, that is, at the time the dose is being injected into the patient's tissue, all of the system elements need to be in communication at the time of dose delivery. The pen needle captures a dose in real time when the reusable sleeve is attached to provide the following functions: (1) receive the sensed data that correlates with the volume of the dose, (2) calculate the dose, (3) time stamp the dose, (4) provide power for the sensor and these functions, and (5) to also simultaneously or at a later time wirelessly communicate the dose and time stamp elsewhere in the IEO dose capture system, such as to the patient's records in the cloud. A replacement pen cap that covers the needle end of an insulin pen and senses plunger movement does sense the movement of the plunger at the exact time of delivery. A pen cap that covers the knob end of an insulin pen and senses the knob movement and travel can preferably capture the real time delivery of the dose, because all the system elements are in communication at the time of delivery.

[0069] To reduce the cost of the disposable MEMS sleeve, the componentry in the sleeve, that is, the MEMS chip and electrical contacts for power and data connections to the informatics enabled pen sleeve is minimized. This device comprises a plastic sleeve into which are assembled the

MEMS chip and the electrical contacts, which are either snap fit, over-molded, or clenched by a retaining component, and a septum, which would be pierced when engaged by the pen needle. These two concepts provide additional benefits as compared to the embodiments described above because they capture the time of the actual delivery as compared to the time of plunger movement to fill a syringe or the displacement in the plunger of an insulin pen sometime after the dose has been delivered, such as when the smart pen cap is placed back onto the pen.

[0070] The above described embodiment is also applicable to an injection port, such as the Patton Medical injection port. The embodiment for use with an injection port may be completely disposable or a combination of disposable and reusable components. Any of the MEMS sensors described above could be spliced into the fluidic pathway within an injection port and the componentry and intelligence that are provided in the informatics enabled sleeve described above would be incorporated into the injection port in the outer perimeter of the port; that is, in the area surrounding the septum into which the syringe would engage. A preferred embodiment for an injection port is a disposable/reusable design in which the disposable portion includes the adhesive, the portion of the housing to which the adhesive attaches, and the components comprising the fluidic path including the MEMS sensor and the electrical connections from the sensor to the informatics enabled reusable portion, which contains all the componentry described above in the informatics enabled sleeve. As discussed above, drug identifying techniques may also be incorporated to verify the specific drug being administered.

[0071] Another embodiment of the invention is illustrated in FIG. 6, which illustrates an informatics enabled attachment 602 for either a reusable or disposable pen 600. This embodiment engages with the adjustment end of the pen. More specifically, a rotational turn knob 604 on the informatics enabled sleeve 602 engages with the adjustment knob (not shown)

on the pen, and the sleeve portion 602 of the informatics enabled attachment slides over and engages with the outer diameter of the barrel of the pen. In one alternative of this embodiment, over-molded metallic splines located axially around the diameter of the knob are used for proximity sensing, similar to a ring counter arrangement that utilizes a proximity sensor to count gear teeth, or splines in this case, as they pass in front of the sensor. In another alternative of this embodiment shown in FIG. 7, a multi-pole magnetic annular ring 702 is used in combination with a Hall-effect sensor 704. The rotational motion and direction of the cap are determined with a rotational Hall-effect sensor or an MR sensor. Determining direction requires a two sensor device such as an Allegro A1233, or a four sensor chip such as an ams AS5304/5306. An AMR sensor requires integration with a single Hall effect sensor to provide direction as well as 360 degree sensing. It should be appreciated that an optical encoder could be used in place of a rotational magnet system.

[0072] FIG. 8 is an illustrative embodiment of a SMART fixed dose pen, for which the intelligence in the system is reduced, i.e. because the dose has been preset and each dose is the same, only the time of actuation / delivery needs to be captured and therefore the Hall-effect sensing arrangements described above are not required. FIG. 9 is another illustration of either an adjustable or fixed dose pen. FIGS. 10 and 11 illustrate embodiments of informatics enabled mechanical patch pens. As used herein, the term “patch pen” refers to a body worn device providing insulin delivery only in a fixed dose each time the user manually actuates the device, primarily utilized for prandial insulin delivery. Preferably a magnetic or metallic flag is incorporated into the mechanization or linkage within the mechanical patch pen. An informatics enabled attachment is integrated into the patch pen, in which case it is disposable, or may be in the form of a separate element that engages to the patch pen, in which case it is reusable. In one

embodiment a motorized "pump engine", that is, a fluid driver used to transfer insulin from the reservoir to the injection/infusion site, delivers 2.0 units per cycle. The motorized pump engine is described in further detail in U.S. Provisional Patent Application no. 61/976,631, filed April 7, 2014.

This pump engine is modified to eliminate the motor and provide mechanization that enables the user to drive the pump engine by squeezing or depressing a button or buttons located on the exterior of the pump, and includes a magnetic or metallic flag located on the linkage within the patch pen, which is sensed by the informatics enabled attachment each time 2.0 units of insulin is delivered manually by the user. Any of the magnetic sensing solutions described above, optical sensing, or any suitable sensing technology, may be utilized for sensing. Additionally, the same pump engine with similar manually driven mechanization may be utilized to actuate delivery in an insulin (or other drug) pen and provides a fixed dose with each actuation, and records the amount and time of each dose.

[0073] Pen cases provide a clean, sealed container in which users can store their injection delivery device and consumables, such as an insulin vial, insulin pen or syringes, pen needles, lancing device and lancets, and alcohol swabs. Pen cases can be either rigid, that is, having a hard exterior shell, similar in design to a jewelry box, or flexible, that is, a flexible pouch, similar to a pencil case. FIG. 12 illustrates an informatics enabled rigid pen case 1200 according to another embodiment of the present invention. The informatics enabled pen case stores the patient's syringe or insulin pen when the device is not being used. A nest or cavity within the pen case is used to register or locate the pen, each time the user places the pen into the case. Each time the pen case is closed, the Hall-effect sensors within the pen case determine the relative position of the plunger and thereby determining the dose delivered to the patient. For a reusable pen, the

insulin cartridge would need to be modified to include a magnetic or metallic flag, such as a washer shaped element with Pressure Sensitive Adhesive (PSA) on one side, that is pressed onto the exposed surface of the stopper in the cartridge, and potentially an RFID chip or some other means, such as a bar code, to convey the ID of the insulin cartridge and the type and concentration of the drug. The magnetic or metallic element is preferably incorporated into the stopper/plunger during manufacturing. In operation, each time the pen is placed into the case, sensors in the pen case scan to detect the position of the stopper and compare the current and previous positions to determine the dose delivered. Data is time stamped, stored within the case and periodically transferred to a smart phone and/or the cloud. One advantage of the pen case is the volume of space available in which to configure the informatics enabling components, which can reduce the cost and improve the performance of the solution by incorporating inexpensive, high-performance components such as off-the-shelf (OTS) batteries, rigid PCBAs, large footprint antennas, an RFID reader, a large user interface (UI) that accepts input from a touch screen, keypad, or from audible commands and provides a display with data, alerts, and warnings for the patient. To enable the use of a flexible pen case, two magnets are incorporated into the syringe or insulin pen, one fixed and the other on the moveable plunger. Each time the pen is placed into the flexible case, the line and relative distance between the two magnets is sensed allowing the dose to be calculated. This concept is also applicable to informatics enabled cartridges utilized in reusable pens and informatics enabled pens that are stored in the pen case, as described above. It will be appreciated that any suitable sensing technology may be utilized, and in particular, magneto-inductive sensing is one alternative suitable for sensing in a pen case. A magneto-inductive displacement sensor operates by using an inductive sensor coil to detect the change in magnetic field as the magnet moves. It is used in head-on sensing with a range of up to 60 mm

depending on magnet size, which is used to detect the position of a magnet incorporated into the plunger piston of an insulin pen or syringe after is placed into a pen case.

[0074] FIG. 13 illustrates an informatics enabled pen case that is further enabled to draw the dose into the syringe. This embodiment of the pen case includes a clamping system 1301 to register the syringe, that is, to precisely locate the syringe on two axes, a nest or cradle to register the insulin vial, and a second clamping system to grip and control the movement of the syringe plunger. In operation, the user places a syringe into the nest adjacent to an insulin vial within the pen case, closes the case, and enters the dose to be delivered into the UI. The two separate clamping arrangements within the case grip the syringe. The first clamp system grips the syringe and advances the syringe to engage the syringe needle into the vial of insulin. The second moves the plunger to draw in the correct dose of insulin. The syringe is retracted from the vial either automatically or by the patient. The same arrangement may be utilized to create a positive pressure within the insulin vial. Orientation or gyroscopic sensors could be used to confirm proper orientation of the pen case for air purge or insulin draw and prompt the user to orient the pen case accordingly. An exemplary smart pen case is described in U.S. Patent No. 7,901,383 .

[0075] As in all embodiments described herein each injection is preferably recorded and time stamped in an electronic logbook, and transferred periodically to a peripheral monitor device such as a laptop computer, cell phone, or other user interface, for review by the patient. Alternately the data could be conveyed via a computer network to and from the cloud to the patient's health care providers. The functionality of the informatics enabled insulin pen case could be further expanded by incorporating auxiliary devices into the system, such as vital signs monitors, fitness monitors or activity trackers, and Continuous Glucose Monitors (CGMs).

[0076] Another embodiment takes the form of an “All-In-One” or combination device. One example of an all-in-one device available on the market is the Dario, by LabStyle Innovations. The Dario integrates a glucose meter, lancet, strip dispenser, and phone application for either IOS or Android into a compact device. Like the pen case embodiment described above, an all-in-one device has sufficient size and volume to incorporate informatics enabling componentry described above to allow an informatically enabled insulin pen or syringe to be attached, that is, by providing a nest or holster for the pen or syringe to be physically and electrically engaged to the all-in-one housing. In this case, the connection provides retention of the pen or syringe and transfer of data. Such a device is described, for example, in U.S. Published Application No. 2011-0054390.

Alternatively, a wireless communication solution such as low energy Bluetooth (BLE) or Near Field Communication (NFC) could be utilized to communicate directly to a Smart phone. An example of a smart phone device communicating with other on body devices in a personal area network is described in U.S. Published Application No. 2011-0022025.

[0077] Another embodiment is an informatics enabled insulin cartridge that is used in conjunction with an informatics enabled reusable pen. The insulin cartridge is modified to include a magnetic or metallic flag, such as a washer shaped element with Pressure Sensitive Adhesive (PSA) on one side, that is pressed onto the exposed surface of the stopper in the cartridge, and an RFID chip or some other means, such as a bar code, to convey the ID of the insulin cartridge, and the specific drug type and concentration. The cartridge would work in conjunction with an informatics enabled attachment for a reusable pen. Alternately, the magnetic field strength could be used to distinguish between different cartridges, eliminating the need for

an RFID chip on the disposable device and an RFID reader within the informatics system. The cartridge is preferably modified during the manufacturing process, following the filling process, or by the patient, either manually or automatically as part of a cartridge filling process designed for home use.

[0078] FIG. 14 illustrates an informatically enabled syringe sleeve according to an exemplary embodiment of the invention. The syringe sleeve 1400 includes a plurality of magnetic position sensors 1402. The syringe 1404 has an embedded RFID chip 1406 and a magnet 1408 that is sensed by the Hall-effect sensors 1402 to determine a dose amount. Of course, as will be appreciated by one of ordinary skill in the art, any suitable sensing method such as those discussed herein may be used in place of magnetic position sensing.

[0079] In another embodiment, external electrodes are attached to the insulin reservoir and a variable capacitance value is sensed based on the fluid level of the reservoir. Electrodes are preferably printed onto any insulin reservoir during manufacturing, and may also be manufactured as a strip that is attached to an insulin reservoir. Alternatively, as shown in FIG. 15, an informatics enabled sleeve 1500 is provided with the electrodes 1502 provided on the inside diameter and which would contact the reservoir when attached to the pen, syringe, vial or patch pump. The electrode 1502 may be printed onto the sleeve or manufactured in any other suitable manner. The electrode 1502 preferably spans a dimension that corresponds to the volume of insulin in the vial. In this embodiment, the sleeve 1500 and strip 1502 are advantageously re-usable. In another embodiment of the informatically enabled insulin vial, the electrodes of a capacitance sensor are incorporated into the vial attachment, such that when the vial attachment is engaged with the vial, the electrode strip is in intimate axial contact with the vial.

[0080] FIG. 16 illustrates an informatically enabled vial sleeve 1600 according to an exemplary embodiment of the present invention. As illustrated, a floating magnetic ring 1602 is provided inside a medicine vial 1604. The ring magnet outer diameter is slightly smaller than the inner diameter of the vial so that the ring freely moves within the vial according to the fluid level within the vial. The ring magnet 1602 is preferably placed into a drug vial prior to sealing the vessel. A typical insulin vial may also be modified to accommodate a rigid magnetic ring, or a flexible magnetic ring may be wrapped in a coil, inserted into a vial through a standard vial neck, allowing the coil to unwind after insertion to a diameter that is smaller diameter than inner diameter of the vial. In the case of an insulin vial, the ring magnet is preferably coated with an insulin compatible material, such as a polymer, which is compatible with insulin and of sufficient thickness and overall buoyancy to enable the ring to float. As illustrated, the level of the ring is sensed by a linear magnetic position sensor, such as a Hall-effect sensor.

[0081] FIG. 17 illustrates another informatically enabled vial sleeve 1700 according to an exemplary embodiment of the invention. In this embodiment, floating magnetic beads 1702 are utilized to sense the level of fluid in a drug vial, such as an insulin vial 1704. A smart vial sleeve 1700 is provided an attached to the medicine vial 1704. The vial sleeve 1700 senses the layer of magnetic beads floating on the surface of the insulin. The beads are of sufficient diameter that they are unable to be drawn into a dose. That is, the beads 1702 are larger in diameter than the needle or cannula or a syringe used to draw insulin from the vial. Advantageously, a user can add the magnetic beads 1702 to any medicine vial post-manufacture, to enable the smart vial sleeve 1700. In one embodiment, the magnetic beads are added to an insulin vial during the filling process in manufacturing. In another embodiment, the filled insulin vial is shipped together with a syringe filled with magnetic beads, the syringe preferably having a large cannula to inject

beads into vial. The cannula of the syringe or other device used to draw insulin from the syringe is smaller than the beads to prevent beads being drawn into the injection device. The number of magnetic beads used is preferably sufficient to substantially cover the majority of the surface of the liquid medicine inside the vial. The vial sleeve attachment utilizes a linear magnetic position sensor, such as a Hall-effect sensor, MR or AMR sensor to detect the level of fluid remaining in the vial according to the position of the floating magnetic beads within the vial.

[0082] FIGS. 18A and 18B illustrate a linear magnetic positioning arrangement 1800 attached externally to a syringe 1802 according to an exemplary embodiment of the present invention. The syringe attachment 1800 conveniently attaches to a syringe 1802, so that a standard syringe may be utilized without modification. A first attachment comprises at least one magnet 1804 that attaches to the syringe 1802, and a second attachment comprises a linear magnetic position sensor 1806, such as a Hall-effect sensor, an MR sensor or an AMR sensor, to detect the position of the magnet(s) 1804. The first attachment 1804 connects to the syringe plunger and the second attachment 1806 connects to the syringe barrel, such that the movement of the plunger is tracked to determine the dose delivered. The smart syringe attachment 1800 preferably recognizes the “home” position of the plunger, that is, the position where the plunger is fully advanced and no fluid delivery is possible. In practice, the syringe plunger may be retracted and advanced many times during a single dose delivery cycle. To identify the movement associated with the dose delivery from other plunger movements, such as the movements used to inject air into the vial, the smart attachment 1800 analyzes the complete cycle of plunger movements each time a syringe is used, and identifies the dose delivered from the final movements, when the plunger advances to the home position for the final time, and from other sensed elements in the dose delivery cycle.

[0083] FIG. 19A illustrates a smart injection port 1900 according to an exemplary embodiment of the present invention. The exemplary smart injection port preferably comprises a lower housing 1902 and an upper housing 1904. The lower housing includes an adhesive surface 1906 to facilitate attachment of the smart injection port to a patient's skin 1908. A septum 1910 is arranged between the upper and lower housings 1902, 1904. The septum 1910 provides access to a cannula 1912 that is inserted into a patient's skin 1908. The septum 1910 may be pierced by an injection syringe, or the like, to inject insulin into the patient through the cannula 1912 without requiring a needle stick for each injection. The smart injection port 1900 includes a MEMS flow sensor 1914 arranged in the flow path between the septum 1910 and the cannula 1912. The MEMS flow sensor 1914 is electrically connected to related electronics located in area 1916 of the injection port 1900. The related electronics include a power supply, processor, and wireless transceiver for transmitting flow measurements to a remote device. Housing 1902 is preferably disposable, and includes the MEMS flow sensor 1914. Housing 1904 is preferably reusable, and includes the related electronics in area 1916. The MEMS flow sensor is preferably a thermal time of flight sensor, but any suitable MEMS flow sensor could be employed.

[0084] FIG. 19B illustrates a conventional single-package MEMS flow sensor 1920. In the single package MEMS flow sensor, the actual MEMS sensor 1922 is combined with related electronics 1924. The MEMS sensor 1922 includes at least one heater, at least one sensor and a flow channel through which a fluid such as insulin flows. The related electronics 1924 are electrically connected to the MEMS sensor 1922 within the single package, and include an integrated circuit, processor, power supply, wireless transceiver chip, and the like.

[0085] FIGS. 19C and 19D illustrate an improved MEMS flow sensor 1930 that includes only relatively low cost disposable parts that should be replaced with each use due to contact with

insulin or the like. As illustrated in FIG. 19C, the MEMS flow sensor 1930 includes an input side 1932 with an input flow tube 1934 through which liquid such as insulin flows to the MEMS sensor element 1936 (shown in FIG.19D). The MEMS flow sensor 1930 further includes an output side 1938 with an output flow tube 1940 through which liquid such as insulin flows from the MEMS sensor element 1936 to downstream elements. As shown in FIG. 19D, the MEMS flow sensor 1930 includes electrical contacts 1942 for connecting the MEMS sensor element 1936 to related electronics, as described above. The related electronics include, for example, an integrated circuit, a processor, a power supply, and a wireless transceiver chip. Because the related electronics are separately packaged, they may be incorporated into a reusable element in an exemplary medication delivery device, thus significantly reducing overall cost.

[0086] FIG. 20 illustrates a system according to an exemplary embodiment of the present invention. The system 2000 includes various components for capturing data and at least one calculating element for receiving data and performing calculations on the data. As illustrated the exemplary system preferably includes a carbohydrate input element 2002, an oral medication input element 2004, and blood glucose monitor (BGM) 2006 and/or a continuous glucose sensor (CGM) 2008. The system preferably includes a wellness data input element 2010. Finally the system preferably includes one of the various embodiments of dose capture device 2016 as described herein. As an example, a smart pen 2016 is illustrated. Together these devices input the significant relevant data needed to monitor a patient with a disease such as diabetes for improved diabetes management. An exemplary carbohydrate input device 2002 can be an app running on a user's cellphone 2011, or the like, which lets the patient input food and drink consumed. Similarly, the same or a related app can serve as an oral medication input element 2004 and permit the user to track oral medications ingested. In addition, the oral medication input element

2004 can be automated to alert the user to take medication, and to confirm and automatically transmit data related to the oral medication taken to the secure hub 2012. The BGM 2006 and/or CGM 2008 preferably communicate blood glucose readings directly to a data hub device 2012. Wellness data can be input by a separate device 2010 or by a related or the same app as described above. The dose delivery information device 2016 according to exemplary embodiments described herein, preferably delivers dose information, such as insulin injected into the patient, in real or near real time. All of the data is received locally by a smart device, such as a cellphone 2011 running the app or apps discussed above. It should be appreciated that while the carbohydrate input element 2002, the oral medication input element 2004, the wellness data input element 2010, the cellphone 2011, and the data hub 2012 are shown as separate elements, all or any combination of them may be combined into a single cellphone or similar computing device. Data is analyzed and calculations are performed locally by the smart device and / or smart phone 2011, and the data hub 2012 is used to transmit data securely, that is, encrypted, to a remote server such as a cloud storage server, and in turn to perform calculations on all of the data received, provide feedback to the user, send all or a portion of the data to a remote health management access point 2020, such as cloud storage, where the information can be accessed by healthcare stakeholders, such as the patient's physician, caregiver, pharmacy, and family. Conversely, alerts, reminders, and interventions can be provided by the user's network, e.g. an HCP, securely through the data hub 2012.

[0087] An embodiment of the present invention includes several features. The first is dose capture, which measures the volume of insulin delivered and a time stamp. This information is preferably captured in a manner that is transparent to the patient. The second is data transfer, which occurs at different interfaces, such as between the dose capture device and the user

interface (UI), or between the patient and health care provider. Additional functions include data transfer to the patient, health care provider, such as a PCP, endocrinologist, or nurse educator, or another risk bearing entity, such as a family member, or diabetes support network. BGM data / CGM data may be incorporated, measured and time stamped. Life style data such as diet and exercise may be captured and considered. Embodiments of the present invention preferably are compatible with fitness monitors and nutrition Apps. Embodiments of the invention preferably include additional intelligence to provide helpful alerts, warnings, recommendations, interventions, intelligent decision making, such as trend analysis, predictions, and therapeutic modifications. Finally, embodiments of the present invention may incorporate or consider oral medication. Preferably, embodiments of the invention are compatible with an oral medication adherence device, such as a Smart pill container.

[0088] Although recent advances in infusion pump therapy have reduced the growth rate of the multiple daily injection (MDI) segment, the overwhelming majority of diabetic patients on insulin therapy continue to receive delivery through MDIs, and primarily with disposable insulin pens.

[0089] The cost of incorporating the necessary components to informatically enable a disposable syringe or insulin pen could be reduced where the informatically enabled portion of the device could be reused, such as in a replacement cap on an insulin pen, or the number of uses of the disposable device could be increased such that the added cost per use would be acceptable, such as a exchanging needle cannulae into a "universal" needle hub. Such a hub is described, for example in U.S. Published Application No. 2012/0041417.

The increase in size of the device is another consideration. Adding an appendage to an insulin pen or modifying the pen cap and creating a larger, less

appealing envelope, such that the modified device needs to be carried in a purse or pack is undesirable. Another issue is creating a universal solution that can be utilized with most currently marketed insulin pens.

[0090] A preferred embodiment that satisfies the above criteria is an informatics enabled insulin pen case, which could utilize a number of different methods to capture the delivered dose, such as taking the weight of the insulin pen each time the pen is placed in the case and the case is closed. The case provides sufficient space to incorporate the necessary electronics, and by having potentially more space than needed, the design can be tailored to utilize inexpensive electronics, such as a rigid PCBA, a disposable battery that has been commoditized, large footprint antenna options for low power data transmission, and ease of assembly.

[0091] In addition to dose capture, informatically enabled medication delivery devices can perform additional functions. For example, an informatically enabled insulin pen with a smart cap can identify particular pen needles for use with the insulin pen. Further, the informatically enabled insulin pen can advantageously reduce or prevent unintended uses. FIG. 21 illustrates a first exemplary system 2100 including an insulin pen 2102, a smart pen cap 2104, a package of disposable pen needles 2106, and a smart phone 2108 running an application. Using the smartphone's camera, the pen needle package barcode 2112 (or any suitable identification) is read by the cellphone. The cellphone 2108 in turn communicates with a cloud-based database 2110 to verify the pen needle package by manufacturer, unit size, lot number, and other factors identified by the barcode. The cellphone 2108 could confirm the barcode validity in real time or near real time, or alternately, could periodically poll the cloud-based database and download a complete list of valid barcodes and associated information such that communication with the

cloud-based storage is not necessary at the time the barcode is scanned. In this embodiment, the barcode 2112 is static and printed on all pen needle packages, and so is subject to reuse.

[0092] In another embodiment illustrated in Fig. 22, the system 2200 includes pen needle packages 2106 that are imprinted with unique barcodes 2202 (or any suitable unique identifier). The cellphone 2108 is used to scan the unique identifier 2202 and communicates with a cloud-based database 2110 to confirm that the unique identifier 2202 is in fact unique and remains valid. Such a system could advantageously be used to assist recalls as needed, and to prevent the use of unauthorized pen needles. In either of the exemplary systems described above, a down counter is preferably set to the number of disposable pen needles in the identified package, and certain functions are restricted after the counter reaches zero, indicating that the package should be exhausted. For example, the smart cap would stop logging delivered doses once the needle package is exhausted, and until a new package is authorized.

[0093] In another exemplary system 2300, a smart sleeve 2302 is provided in each package of disposable pen needles 2106. The smart sleeve 2302 is connected to the pen needle, and the smart sleeve contains an RFID chip. The RFID chip may be read by either the smart cap 2104, or the cellphone 2108, to verify the pen needle package. Advantageously, the smart sleeve 2302 is read by the smart cap 2104 each time the cap is placed on the insulin pen 2102. If the smart cap 2104 reads the RFID chip, the chip information is preferably transmitted to the smartphone 2108, which in turn communicates with a cloud-based database 2110 as discussed in the above described examples. RFID chips preferably include lot information, manufacturing date, and any other suitable information, and do not require printing space on the pen needle package. Similar to the example provided above, a down counter is preferably provided to restrict higher level functions once the disposable pen needles provided in the package 2106 should be exhausted.

The smart sleeve 2302 preferably forms an interface between the insulin pen 2102 and pen needles using the existing threaded interfaces on the pen and pen needles. That is, the sleeve includes inward facing threads to mate with the insulin pen 2104, and outwardly facing threads to mate with the disposable pen needles. In one version the smart sleeve includes a septum and a cannula, and forms part of the flow channel between the insulin cartridge and the pen needle. In this version, the smart sleeve preferably includes a flow sensor such as a MEMS flow sensor discussed above. In another version, the pen sleeve merely contains identifying information, such as an RFID chip to identify the lot number, number of units, and other information of the disposable pen needle package. In this version the smart sleeve still includes inwardly facing and outwardly facing threads for mating with the pen and pen needles, respectively, but the sleeves forms a hollow cylinder and although the pen needles mate with the smart sleeve, the inwardly facing cannula of each pen needle still pierces the septum of the insulin pen, such that the smart sleeve does not form part of the fluid path between the insulin cartridge and the pen needle.

[0094] In another exemplary system 2400, a smart cap 2104 is provided with a bank of emitters 2402 and a bank of sensors 2404. A portion of the emitters 2402 and sensors 2404 sense the location of the plunger in the pen needle before and after an injection to verify the dose delivered to the user. At least one other emitter and sensor are located adjacent to the pen needle 2406 such that when the smart cap 2104 is attached to the pen 2102 the smart cap can identify the pen needle based on a signal received by the sensor. The smart cap 2104 communicates with the cellphone 2108, and the cellphone 2108 communicates with a cloud-based storage 2110 as discussed above. In this embodiment, proprietary disposable pen needles are advantageously marked such that the emitter and sensor recognize a unique signal identifying the pen needle as authentic. The signal may be optical, magnetic, or any other suitable signaling means.

[0095] In yet another exemplary system, all of the features above are combined. That is, the disposable pen needle package 2106 is imprinted with a unique barcode 2202 (or any suitable marking), the package of pen needles 2106 is provided with a smart sleeve 2302, and the disposable pen needles are manufactured with a unique signature, such as an optical, magnetic, or any other suitable signature signal. The smart cap 2104 triggers a down counter in the smart sleeve 2302 or the smartphone 2108, and senses the unique signature of authentic pen needles. If the pen needle is not recognized some or all functions may be restricted as discussed above. A down counter is used to restrict higher level features once the package of pen needles should be exhausted.

[0096] A further embodiment including a rotary dose adjustment knob or dial will now be described. As illustrated in FIGS. 25 and 26, an embodiment of the invention 2500 preferably attaches to a commercially available insulin pen, using a press-fit feature to hold and translate the rotary knob used to dial insulin dose before injection. Another means of attachment may be a disposable plastic ring with customized internal features that would mate with a specific commercially marketed insulin pen and external features that would be common across all rings and would mate with the rotary device. The body of the device 2500 attaches to the insulin pen body and keeps the sensor 2502 stationary relative to the rotary pen body. An inner sleeve translates axially as a rotary knob 2504 rotates, while an outer sleeve 2506 remains stationary and provides a hand hold for the user. The outer sleeve is preferably held stationary on the insulin pen body using a locking collar that is tightened by a partial turn knurled nut, sliding “push on” connector, or any other suitable single motion actuator to lock the collar.

[0097] A 360 degree dial 2504 of the rotary device holds a ring magnet 2508 with a total of 36 poles (alternating North and South, measured 2mm wide each on the median diameter). Of

course the number of poles of the ring magnet may be altered without departing from the scope and spirit of the invention, and the number 36 should be considered a preferred embodiment. The device holds an off-axis hall effect encoder, such as an AS5304 sensor manufactured by ams ag, in a position to observe the ring magnet. The device translates axially (telescoping) along with the extension of the rotary knob as a dose is dialed. The magnet is preferably located 1.5 mm above the sensor and oriented so that the median diameter of the ring magnet aligns with the hall elements of the sensor chip. As the dial 2504 is rotated, it directly translates the internal dose selection knob and rotates the ring magnet 2508 with respect to the sensor 2502. Software records all motion of the device dial. The device 2500 incorporates a button feature to translate injection force during injection delivery to a free-spinning push button or actuator on the top of the insulin pen. The button uses the magnetic field measurement built in the sensor to recognize the start and end of a dose. This is preferably achieved by using the force from dose administration to offset opposing plastic springs and move the magnet closer to the sensor. As the magnet moves closer, the analog voltage reading of the magnetic field passes a predetermined threshold set in software. An LED incorporated into the rotary device is preferably turned on to show the user that the magnetic switch has been activated and rotation is being recorded.

[0098] All rotation data, both clockwise and counter-clockwise, is preferably stored and processed to correctly record doses delivered from the insulin pen. Time and date information is also preferably stored with each dose entry. The dose reading is calibrated from angular rotation of the dial. The sensor and ring magnet, with 36 magnetic poles, is capable of 2880 counts per rotation, which corresponds to 20 insulin units. This yields a resolution of 0.007 insulin units, with an average error of less than 0.5 insulin units seen during laboratory testing.

[0099] According to this embodiment, rotation of an insulin pen dial is sensed to accurately track the intended dose. To translate rotational tracking to dose monitoring, an analog voltage supplied by the sensor indicates magnetic field strength. A threshold is set in software, to recognize when the thumb force has reached a level that would begin a pen injector dose. Plastic springs or another form of spring is used to hold the ring magnet greater than 1mm from the sensor when no force is exerted on the pen injector actuator. As force is exerted, the spring is depressed and the magnet moves closer to the sensor. As the magnetic field is increased, the device can differentiate dose injection movement from dialing movement. Without a method to differentiate between dialing and dosing, the efficacy would be comprised by false positives in which the user dials back and forth without injection. This embodiment uses an off-axis stationary sensor and a multi-pole ring magnet embedded in the rotating dial. Most insulin pens have dose adjustment in 1.0 unit increments, and a small percentage of commercial injection pens have 0.5 unit incremental adjustments. The resolution and accuracy provided by exemplary embodiments of the invention advantageously exceed the accuracy of the pen, and therefore enables accurate measurement of the intended dose delivered by the patient. Alternately, clockwise (CW) and counter clockwise (CCW) rotational movements could be summed to determine the dose. This embodiment eliminates the need to add undue height to OTS pen injectors, permitting users to operate the combination pen and device more easily. The device preferably contains a PCB, battery and ring magnet along and around the pen injector body to conform with a natural hand hold, as shown in FIG 27.

[00100] A linear dose measurement device according to an exemplary embodiment of the invention will now be described in connection with FIG. 28. In one version an array of anisotropic magneto-resistive (AMR) sensors and a single Neodymium magnet are incorporated.

In another version a single linear hall encoder measures the displacement of a strip magnet with 28 poles alternating North and South, each pole measuring approximately 2mm. In both versions a syringe is inserted into and constrained within the body 2802 of the linear device 2800, and the syringe plunger 2804 is retained within a “follower” 2806, which is an element of the linear device 2800 that translates the movement of the syringe plunger to the sensor(s) within in the linear device. The body 2802 of the linear device has a cavity or nest 2810 that receives the syringe 2808. The cavity can be sized to receive only one diameter of syringe or the cavity can be universal to accept many diameters of syringe, in which case, the syringe diameter can be identified through one of (1) scanning of a bar code on the outer surface of the syringe, or (2) using the optics within a smart phone to measure the barrel, or (3) an RFID chip could be incorporated into the syringe, such as by over-molding, and the linear device 2800 could read the RFID through means of Near Field Communication (NFC), or others means.

[00101] The first version uses a neodymium magnet 2812 to travel 55mm translating the position of a plunger 2804 within a syringe 2808. An array of sensors is placed on a line parallel to the magnet path at a 10mm offset and observes the magnetic field emitted from the magnet. The array preferably has 6 AMR sensors (Honeywell HMC1501) spaced at 10mm intervals. As the magnetic field increases due to magnet proximity, a voltage is induced and recorded. The system is calibrated to merge all sensor data and output the linear position of the magnet. Insulin dose is calibrated from the linear position of the magnet and the cross sectional area of the syringe it is tracking. In one example, a 1mL syringe is used with a 55mm travel, which translates to 18.18 insulin units per mm.

[00102] The neodymium magnet is captured within the device using a slide 2806 that connects to and replaces the thumb actuator 2814 of the syringe plunger 2804. As the plunger

2804 moves linearly to draw fluid into the syringe, the magnet 2812 also moves in direct axial translation. The body of the syringe 2808 is held in place by clipping it into the device 2800 and finger holds 2816 are held to prevent axial translation. The sensor array and magnet are separated by a 10mm gap, which provides room for 1mL and smaller syringes, with all critical parts set coplanar. A rear cover 2818 is connected to the body 2802 of the device using fasteners 2820, or the like.

[00103] The linear hall encoder version has a similar form factor to the AMR approach. It positions the Hall sensor within the body 2802 of the device 2800, giving less than 0.8mm separation from a strip magnet. The strip magnet is 55mm in length, glued to a slide 2806 that connects to and replaces the thumb actuator 2814 of the syringe plunger 2804. This slide 2806 will also translate axially directly with the plunger 2804 as fluid is drawn in or injected from the syringe 2808.

[00104] The linear hall encoder uses a home position to determine when the syringe plunger 2804 has reached the 0mL position. To accomplish this, the end of the strip magnet is placed 1-2mm before the total slide 2806 travel has finished. This causes a drop in 2 of the 4 hall elements sensing, which triggers a magnetic strength error. By knowing the travel required to reestablish sensing of the first pole pair, a zero position can be calibrated. Alternatively, the zero position can be determined by placing ferrous material at the zero position to change the magnetic field in a unique way. This allows the linear hall encoder to record absolute measurement, which increases performance and eliminates offsets that can be introduced by sequential error. An LED is preferably employed to inform the user that the device recognizes motion away from the home position and is recording the position of the plunger. If a multicolor

LED is used, one color may be used to indicate drawing medication and a different color can indicate injection as the device 2800 tracks both directions of travel.

[00105] Priming movements are preferably recognized by means of an accelerometer and/or software that rationalizes all the movements of a delivery cycle to determine the actual dose delivered to the patient, such as the final plunger movement before the syringe returns to the home position is the dose delivered.

[00106] A continuous flow rate tracking device 2900, illustrated in FIG. 29, will now be described. The continuous flow rate tracking device 2900 uses a MEMS Thermal Time of Flight (TToF) liquid flow sensor to record the flow rate through a cannula adapter 2902. This adapter attaches onto a commercially available insulin pen or is incorporated into the design of an insulin pen and allows for the attachment of a traditional insulin pen needle 2904.

[00107] The adapter is primed with the same process that is used with a traditional pen needle, using less than 5 insulin units. A switch to trigger the sensor "ON" is incorporated into the pen cap 2906. In one embodiment, the switch is operated in conjunction with an accelerometer to measure movement of the device/pen and enter a low power mode from a sleep mode after the device is set aside for a period of time. Flow rate is recorded by using sinusoidal heat waves generated on one thermistor and measuring the amplitude and phase shift seen on a downstream thermistor. The flow rate is integrated with respect to time to calculate dose volume.

[00108] Most of the device 2900 is built into a durable assembly that can be reused with many insulin pens and flow adapters over a one to two year period. Preferably, only the pen needles 2904 will need to be disposed of after each use and the flow channel adapter 2902 will be disposed of when each insulin pen is discarded. The flow channel adapter 2902 has a male

and female end that are identical to the male connection feature on the end of an insulin pen and the female connection hub on a pen needle 2904.

[00109] The flow sensing device 2900 can be used to promote adherence or conformance to procedure, that is, following the guidance described in the Forum for Injection Technique (FIT), which was developed to establish and promote best practices in injection technique for all involved in diabetes care. The flow sensing device 2900 preferably utilizes a Real Time Clock (RTC) and a rolling event finder to store only dose event data on the Thermal Time of Flight (TToF) durable device. The event finder will have a “dose start” and “dose end” time stamp. An LED can be used and illuminated when the dose is being delivered and measured, and the LED can remain on for a specific number of seconds after the “dose end” event is sensed. Alternately, a piezoelectric vibratory device may be incorporated into the system to provide tactile feedback to the patient. The flow sensing device 2900 also includes an accelerometer (not shown) to distinguish random movements of the pen from dosing events. The flow sensing device 2900 can therefore be used to determine whether or not the patient holds the insulin pen to their tissue for the recommended duration after the dose has been delivered, that is, the device can advantageously measure conformance to procedure. Non-conformance can be noted in the patient’s electronic logbook, which can be evaluated by the Health Care Professional (HCP).

[00110] In the case of extreme non-conformance, such as the patient removing the pen from the tissue before the dose has been completely delivered, a surge in flow will be detected by the flow sensor. An alarm can be incorporated into the device to alert the patient of an incomplete dose. Both the intended dose and the portion of the dose delivered into the tissue are preferably recorded into the patient’s logbook, along with any correction dose, allowing the HCP to identify this shortcoming in the patient’s self-therapy. For extreme cases of non-conformance,

where the patient is continually receiving less than the intended dose, the HCP can be notified directly to intervene and provide guidance.

[00111] The TToF sensor can also advantageously detect back flow, which could be caused by occlusion of the cannula or excessive resistance to flow as a result of the patient mistakenly injecting into the intradermal space. In both cases, an alert is sent to the patient, prompting the patient to confirm whether proper and complete dose delivery has occurred. This feature is also useful for infusion of subcutaneous or intravenous medications in either an ambulatory or clinical setting.

[00112] One of ordinary skill in the art will appreciate that modifications to the electronic circuitry and software may be made to improve the device and provide additional advantages, such as incorporating a Bluetooth Low Energy (BLE) chip with Near Field Communication (NFC) capabilities. Such additions would enable the system to identify Pen Needles (PNs), which include an NFC tag, for example.

[00113] Another dose measurement device 3200 using thermal time of flight to measure doses will now be described in connection with FIGS. 32-42. As illustrated in FIG. 32, the device 3200 works in conjunction with a standard insulin pen 3202. A dose sensor disposable portion 3204 is connected to the insulin pen 3202 where a standard pen needle 3206 would normally connect. A dose sensor durable portion 3208 fits over the disposable portion 3204. The pen needle 3206 threads onto a distal end of the disposable portion 3204. Finally, a cap 3210 fits over the durable portion 3208. The dose sensor durable portion 3208 preferably includes electronics, and in particular wireless communication components, to wirelessly communicate and exchange data with a smart phone 3212, or any other suitable remote device.

[00114] The dose sensing disposable portion 3204 described above utilizes an anisotropic (z-axis) thermal film to transmit a heat signal for a thermal time of flight flow sensor that is part of a dose capture system used with a standard insulin pen. Disposable portion 3204 will now be described in greater detail in connection with FIGS. 33-35. The disposable portion 3204 includes a z-axis film 3212, a plastic manifold 3214 that is used to create uniform laminar flow in the vicinity of the sensor, an inlet cannula 3216 that pierces the septum of a standard insulin pen and a rubber septum 3218 on the discharge end that accepts a standard insulin pen needle. On the inlet end, a threaded or snap-fit portion 3220 is adapted to connect to a standard insulin pen 3202. As illustrated in FIG. 35, when assembled the surface of the z-axis film 3212 protrudes into the flow channel to ensure that the shear and velocity gradients across the surface of the film are steady, and that there are minimal fluid stagnation zones.

[00115] The durable portion 3208 is illustrated in exploded view in FIG. 36. The durable portion 3208 comprises a battery 3222, a circuit board 3224 including wireless communication components (not shown), a MEMS based thermal time of flight sensor element 3226, plastic housing 3228, and additional components 3230a, 3230b to engage the sensor 3226 to the disposable portion 3204 and also lock or clamp the durable portion 3208 onto the insulin pen 3202.

[00116] The dose sensor described above calculates insulin volume by analyzing data received from the sensing element. The time delay for heat pulses to travel from an input heating element to a downstream sensing element are preferably used to determine a phase shift. The magnitude and phase shift of measurements at the sensing element are preferably used to determine insulin flow. Additional details on the thermal time of flight sensor element are shown described in connection with FIG. 37. The sensing element 3226 consists of a MEMS chip

bonded to a circuit board. The MEMS chip is a ceramic or glass substrate with conductive traces for a heater 3230 and two symmetrically offset temperature sensing elements 3232. The center heating element 3230 is heated via electric current, and the two outside elements 3232 are used to measure the thermal signal created by this heater. The circuit board provides structural support and makes electrical connections to the MEMS sensor chip. The two sensing elements 3230 are preferably symmetrically offset from heating element 3230. Modifying the offset distance permits selection of a particular flow rate range that exhibits large phase resolution, yielding better accuracy. In addition, multiple sensing element pairs may be provided at different offset distances, such as 100um and 200um, to extend dose measurement accuracy to larger flow rate ranges as needed.

[00117] FIG. 38-40 show the interactions between the disposable portion 3204, the durable portion 3208, the insulin pen 3202, and the pen needle 3206. The disposable portion 3204 is assembled onto the insulin pen 3202, piercing the rubber septum on the insulin pen and creating a flow path. The durable portion 3208 is then assembled onto the disposable portion 3202 and the thermal time of flight flow sensor in the durable portion 3202 is pressed against the surface of the z-axis film 3212 in the disposable portion 3202 so that the two components are in intimate contact with no gap between them. This mating condition, illustrated at 3234 can be made via a secondary step, such as pressing a button 3236. The sensor 3226 can alternately be mounted to a spring loaded arm or cam so that it is done automatically for the user. The components in the durable portion 3208 are designed with compliance to allow for tolerance stack up between the sensor 3226 and the disposable portion 3208. FIG. 38 shows the sensor 3226 pressed against the surface of the z-axis film 3212. FIGS. 39-40 show cross sections through the flow sensor with the two components mated.

[00118] FIG. 41 shows a close up of the cross section of the z-axis film 3212. The film 3212 is a composite of thermally conductive particles, flakes or fibers embedded in a low thermal conductivity surrounding matrix. The composition of the film allows for relatively high thermal conductivity in the direction perpendicular to the plane of the film and much lower thermal conductivity in the direction along the plane of the film. FIG. 42 illustrates the intended heat flow path during sensor operation. The heater 3230 sends pulses of heat through the film 3212 and into the fluid 3234, where it is carried downstream by fluid flow. The heat is then conducted in the opposite direction through the film to the thermal sensor 3232. The ideal z-axis film will have minimal thermal resistance in the Z direction while having relatively high thermal resistance in plane (XY).

[00119] The device described above preferably has the following characteristics. The z-axis film 3212 should be as thin as possible. The volume fraction of thermally conductive particles should be as high as possible, while allowing for separation between the particles to minimize in-plane conductivity. The thermally conductive particles should be evenly spaced at a pitch that is much lower than the spacing between the heater and the sensor. The particle thermal conductivity should be as high as possible. The surrounding matrix thermal conductivity should be as low as possible. An ideal particle would have a cylindrical shape with a small diameter and a length that would span the thickness of the film. The particles should preferably extend beyond the surface of the non-conductive matrix material in order to minimize thermal resistance. The films should be elastic or slightly compliant so that it can conform to the surface of the MEMS sensor and eliminate air gaps in order to minimize thermal resistance at the interface without cracking, fracturing or leaking. Pressure from the fluid channel would ensure that the film was firmly pressed against the surface of the MEMS chip during operation and minimize thermal

contact resistance. The z-axis film sheet preferably bonds to ABS or other common thermoplastics. A hermetic seal is required between the film and plastic manifold. The z-axis film would ideally have a light tack, so that it sticks slightly to the surface of the MEMS chip, but can be peeled away completely with no residue or torn pieces remaining on the surface of the MEMS chip. The z-axis film should be stable when exposed to insulin for up to five days, and must not release harmful substances into the fluid stream. Biocompatible coatings or surface treatments may be applied to the base of the z-axis film to improve insulin and biocompatibility. Examples of z-axis films presently manufactured, and potentially suitable for use with embodiments of the present invention include Adhesives Research (EL-9032), 3M (9882), Btech (TP-1), Shin Etsu (Type AF) and Shin Etsu (Type MAF).

[00120] Embodiments of the invention have several potential advantages. First, embodiments of the invention allow the MEMS sensor to be moved from the disposable to the durable portion of the dose sensing system, thereby lowering the cost of the system, and also potentially permitting a higher precision sensor to be used, since the sensor cost is spread over many uses. Embodiments of the invention also isolate the sensor from insulin contact and allow all electrical connections to the sensor to be permanent.

[00121] One variation of the above described embodiment combines the manifold with the pen needle. The advantage of this configuration is that it eliminates the disposable portion of the sensor. The disadvantage of this configuration is that it increases insulin waste due to the need to prime the sensor channel with each injection.

[00122] In another embodiment combining the manifold and pen needle, it is possible to utilize 3D printing to fabricate both the pen needle body and the incorporated Z-axis film “window”. Notwithstanding, 3D printing can be utilized advantageously to fabricate a Z-axis

film for a standalone manifold. There are a number of 3D printing technologies that could be utilized. One example is FDM (fused deposition modeling), also known as FFF (fused filament fabrication). Here, thermally conductive polymer filaments are used to print thermally conductive approximately 100 micron diameter columns in the Z axis film; the necessary diameter depends on the separation between the heater 3230 and the sensing elements 3230 and the widths thereof in FIG. 42. The matrix of the film is printed using a low thermal conductivity polymer (unfilled) material. In one embodiment of the 3D printed Z axis film, the structure is built up on a very thin (25 micron or thinner) compliant polymer film, which will be the side that contacts the MEMS flow sensor. The advantage of this is to ensure a liquid-tight Z-axis film and also providing a compliant substrate for low thermal resistance attachment to the MEMS flows sensor, whereas the disadvantage is in having a small thermal conductivity penalty in the Z direction.

[00123] In yet another embodiment, the z-axis material could be configured as a tube, so that the film forms the complete flow path and a secondary manifold is not required. For example, the z-axis tube may be overmolded into the body of the pen needle, and if required, could be reshaped, such as into a square or rectangular cross-section to provide a flat surface to more easily mate with the heater and sensor traces. The disadvantage of this configuration is that it is more difficult to make good contact between the sensor and the z-axis film tube.

[00124] The dose sensor described above could also be used with other flow sources, such as infusion pumps, syringes, or gravity fed infusion lines, in addition to use in connection with insulin pens.

[00125] Although only a few embodiments of the present invention have been described, the present invention is not limited to the described embodiment. Instead, it will be appreciated

by those skilled in the art that changes may be made to these embodiments without departing from the principles and spirit of the invention.

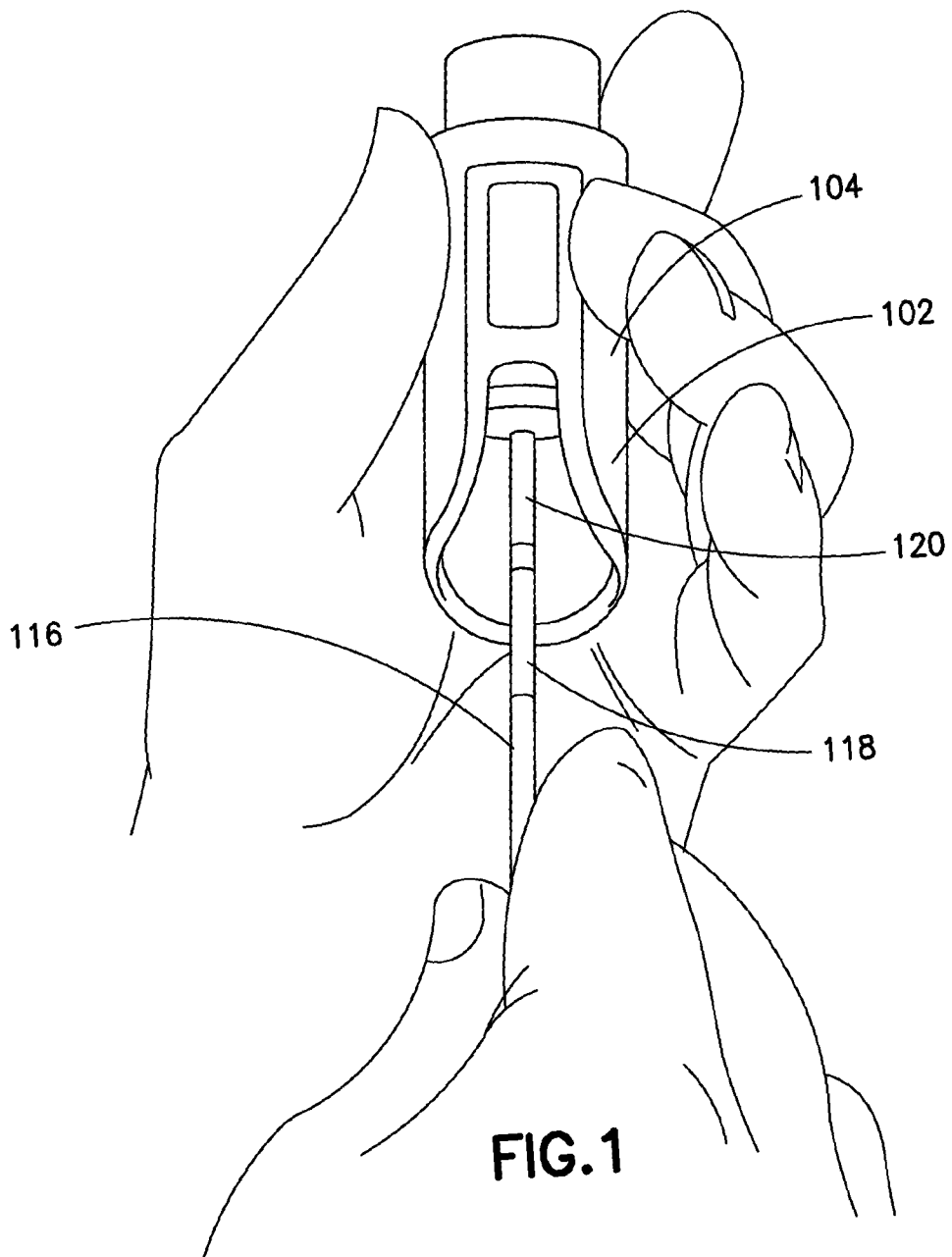
Claims

1. An informatically enabled dosing system for improved treatment of diseases comprising:
an insulin dose input element;
an oral medication input element;
a blood glucose level input element; and
a carbohydrate input element;
wherein the system further comprises a data hub adapted to receive data from each of the input elements to perform calculations based on the data received from the input elements, and to provide feedback to a user based on said performed calculations.
2. The system of claim 1, wherein said insulin dose input element comprises a smart dose determination device comprising a transceiver adapted to transmit substantially real-time dose information to the data hub when a dose is administered to a user.
3. The system of claim 1 wherein the oral medication input element comprises an informatically enabled oral medication container that communicates to an application running on a smartphone, adapted to receive a user input corresponding to an oral medication amount taken by the user.
4. The system of claim 1, wherein the blood glucose level input element comprises a blood glucose monitor comprising a transceiver adapted to transmit blood glucose data to the data hub.
5. The system of claim 4, wherein the blood glucose monitor is a continuous glucose monitor.
6. The system of claim 1, wherein the carbohydrate input element comprises an application running on a smartphone, adapted to receive a user input corresponding to food and/or drink ingested

by the user, and wherein the application is adapted to estimate carbohydrates ingested by the user from the user input.

7. The system of claim 1, further comprising a wellness data input element.

8. The system of claim 7, wherein the wellness data input element comprises an application running on a smartphone and adapted to receive user input related to wellness data and to transmit said wellness data to the data hub.



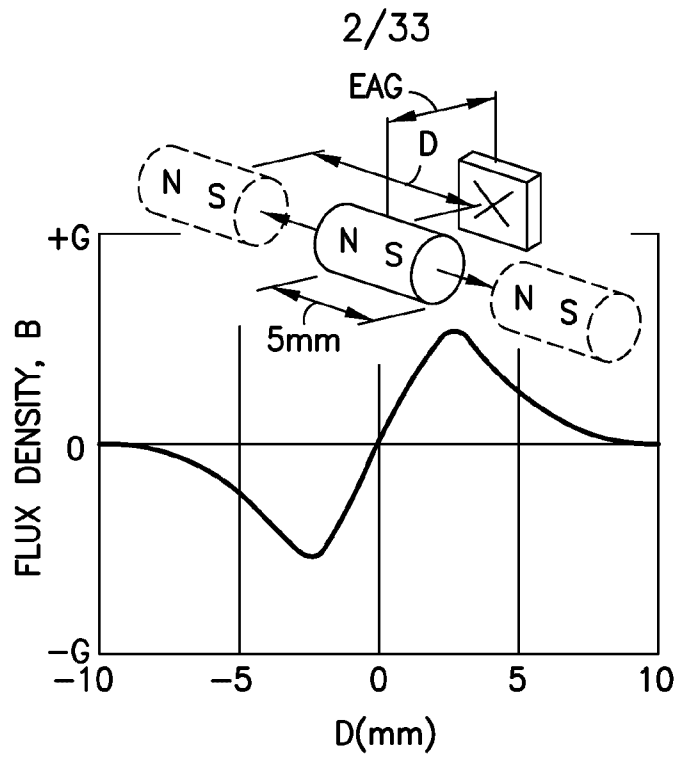


FIG.2A

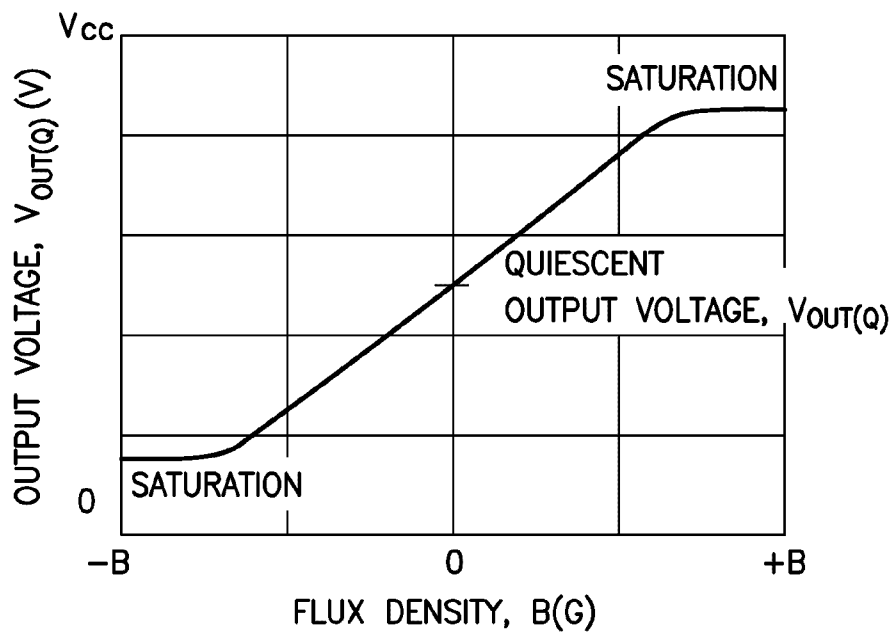


FIG.2B

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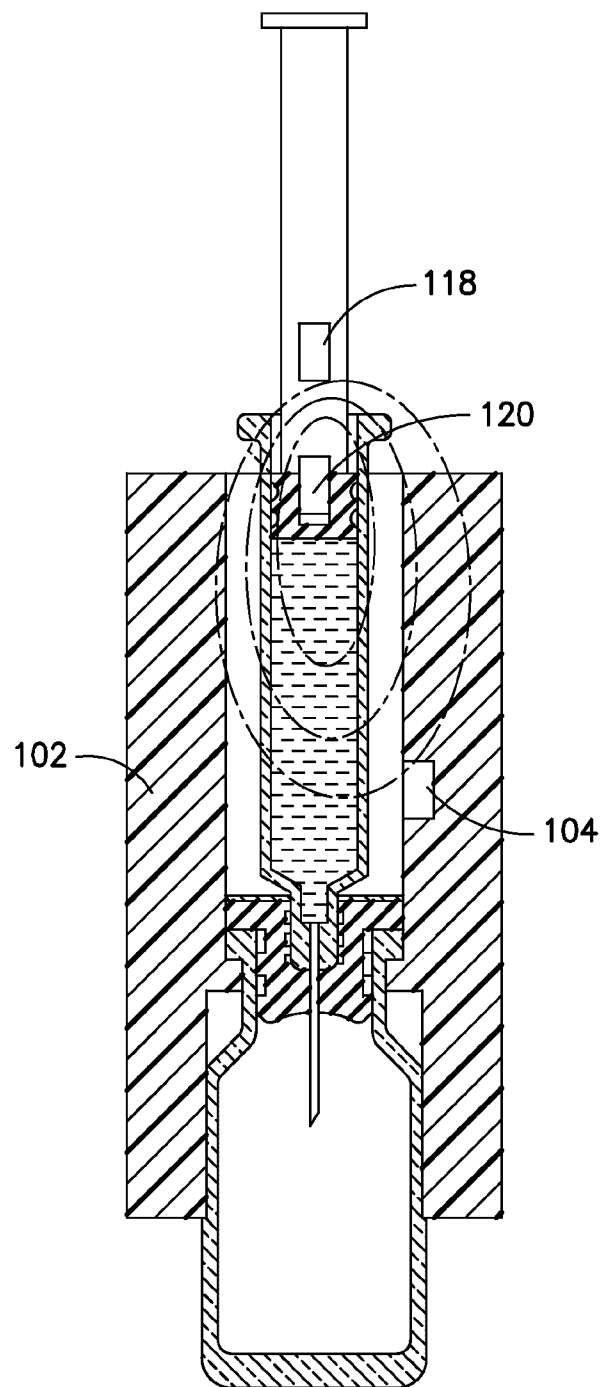


FIG.3

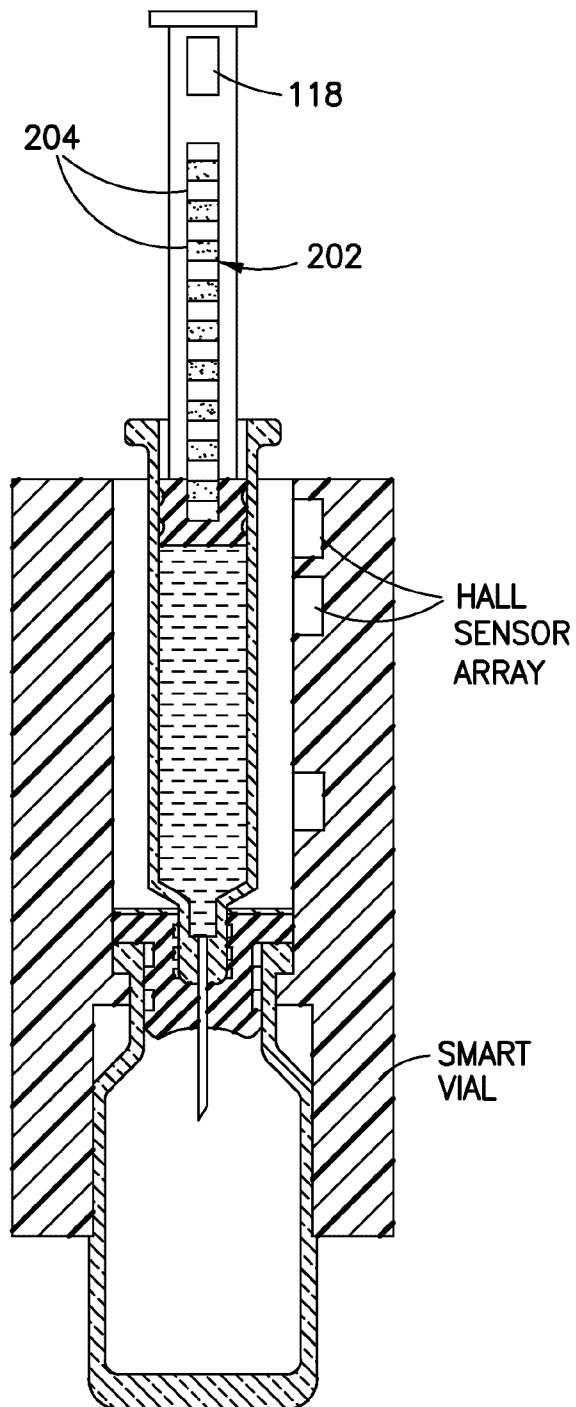


FIG.4

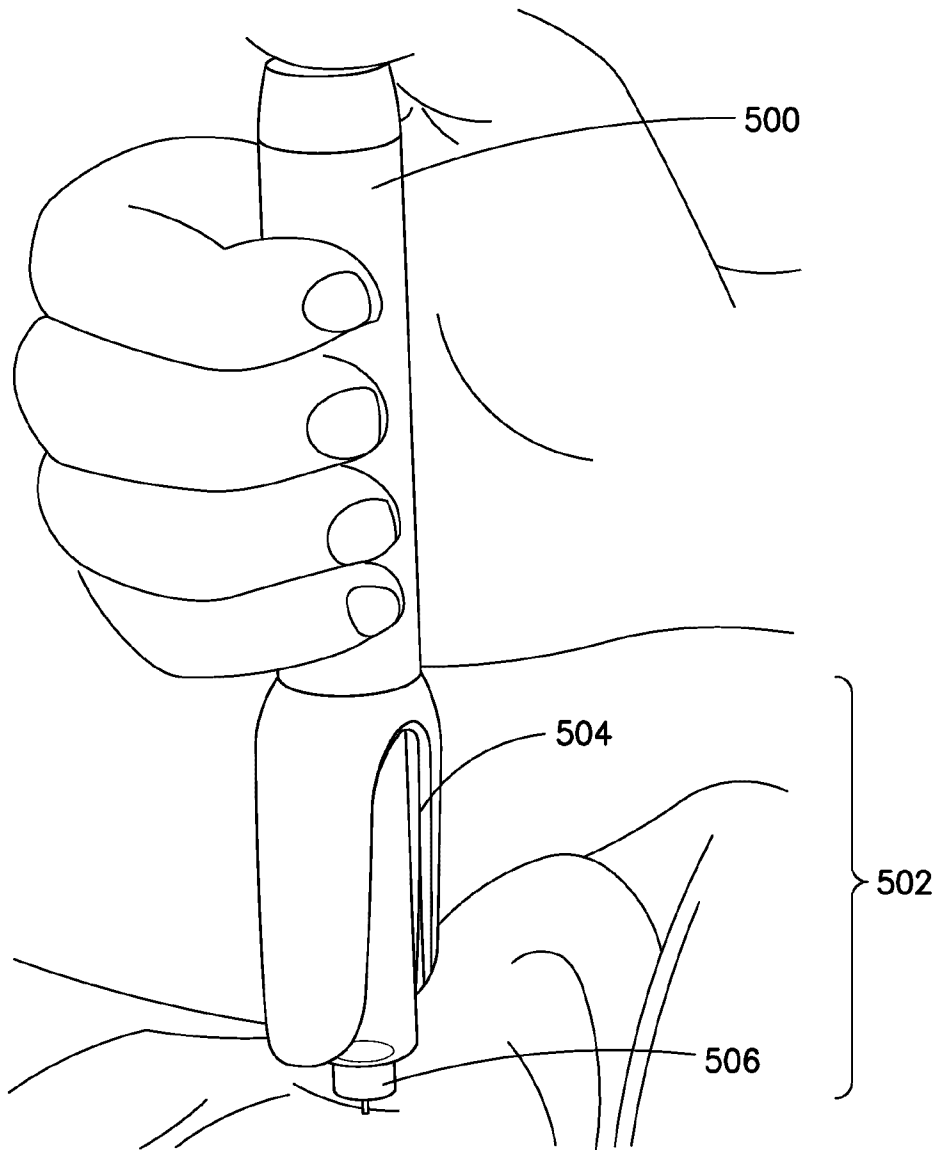


FIG.5

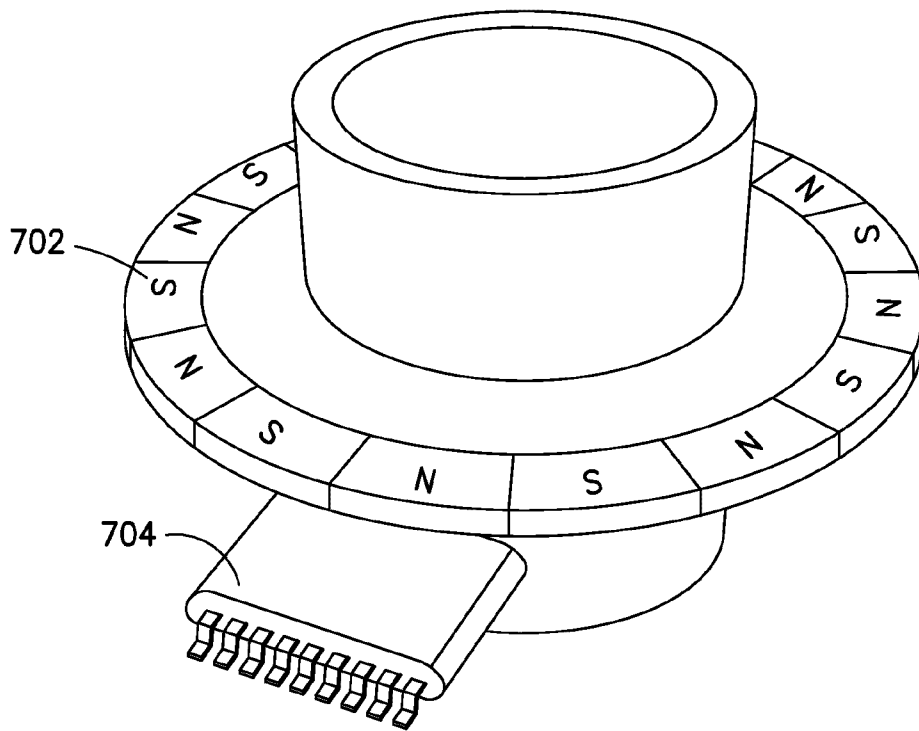
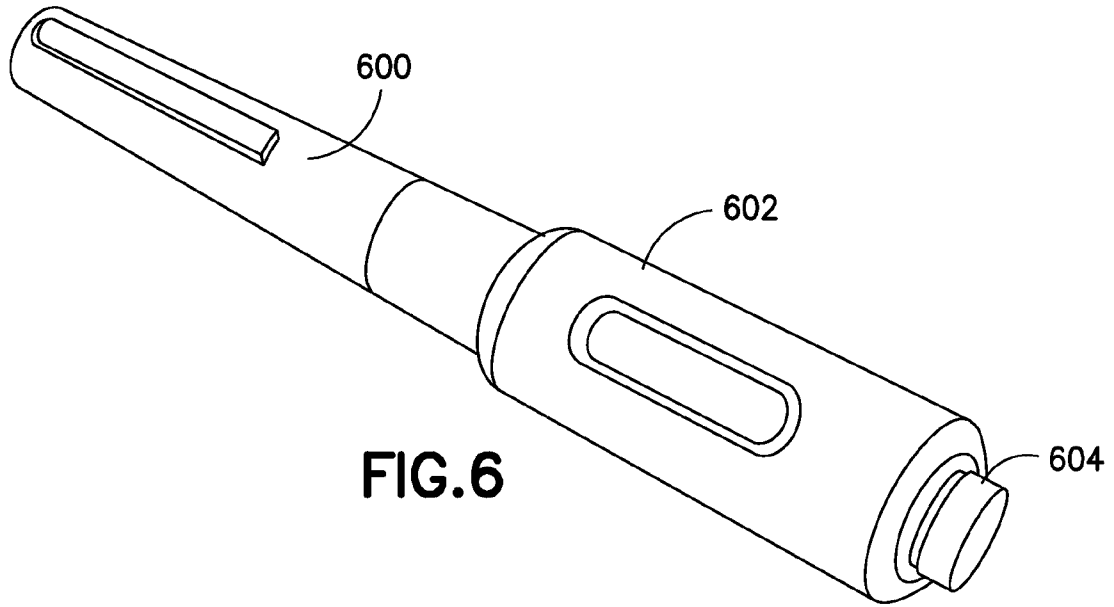


FIG.7

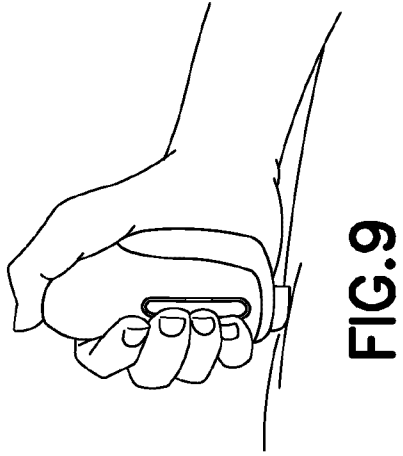


FIG. 9

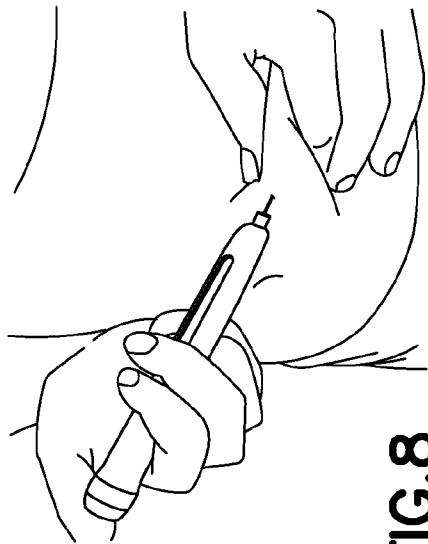


FIG. 8

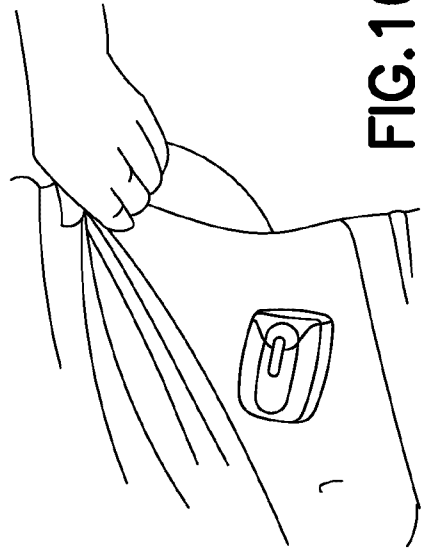


FIG. 10

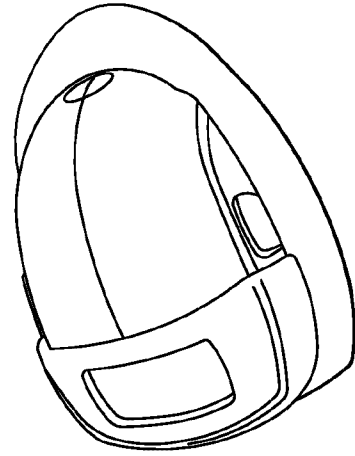


FIG. 11

FIG.12

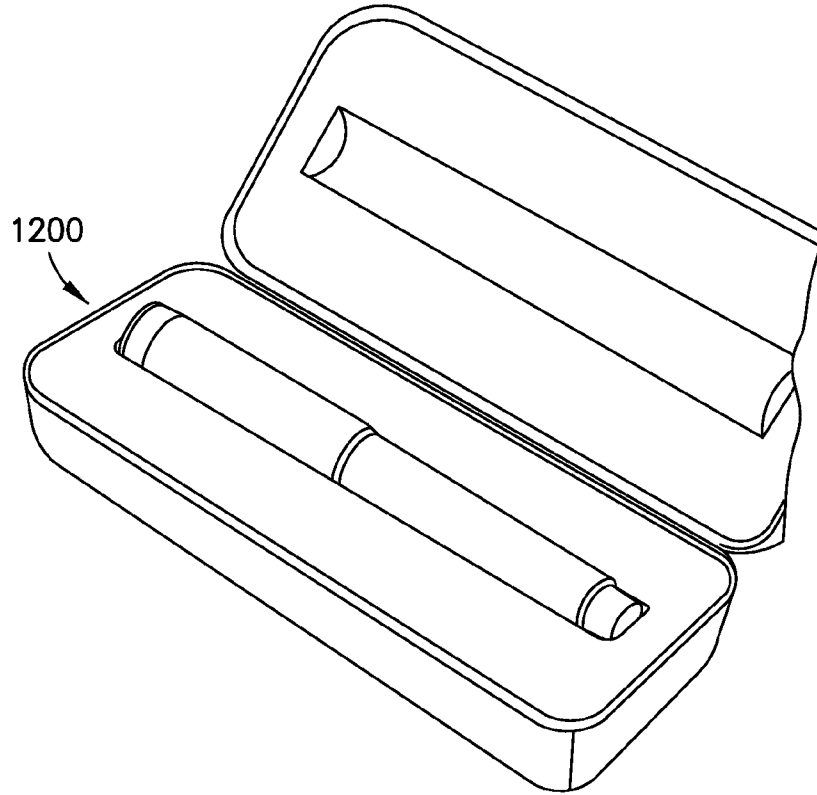
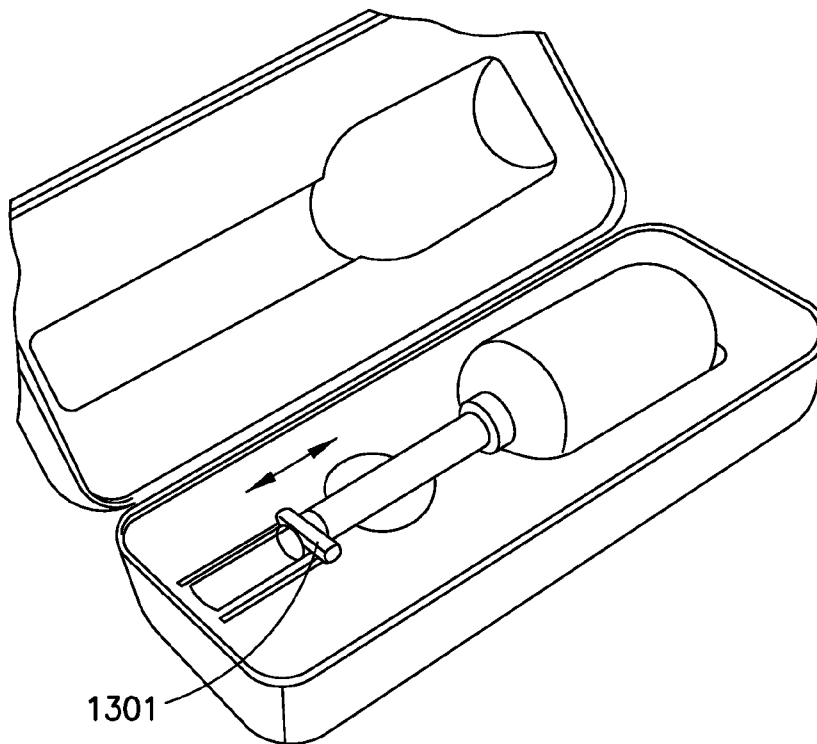


FIG.13



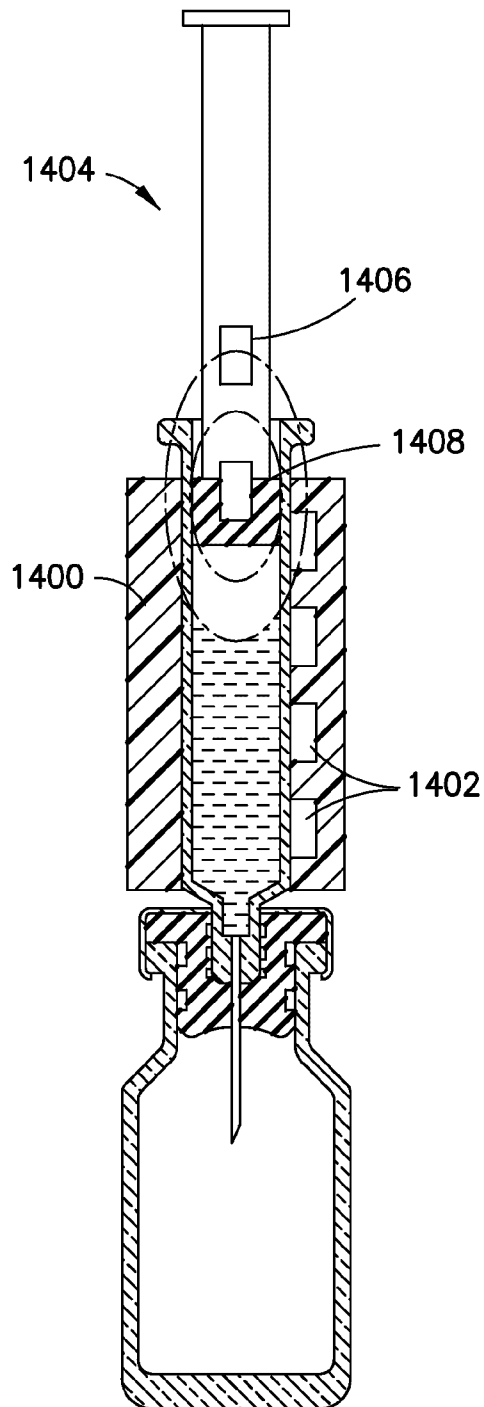


FIG.14

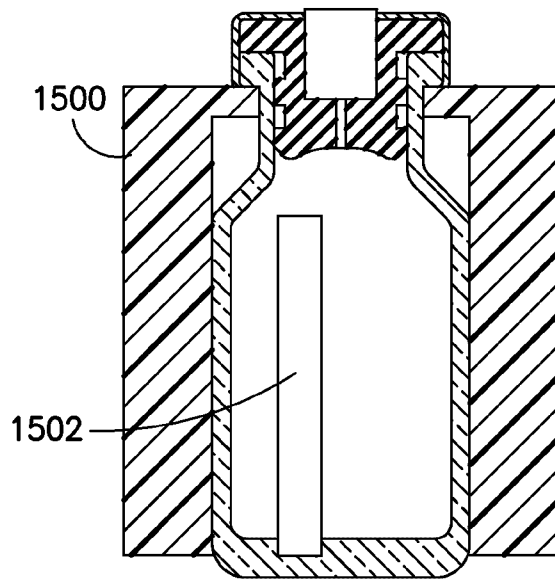


FIG. 15

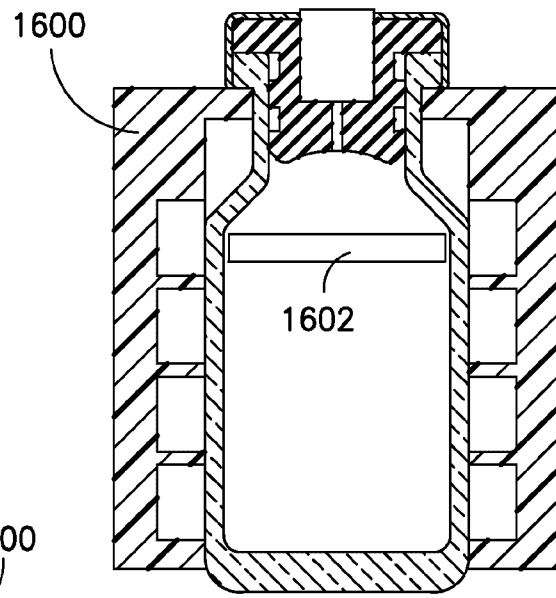


FIG. 16

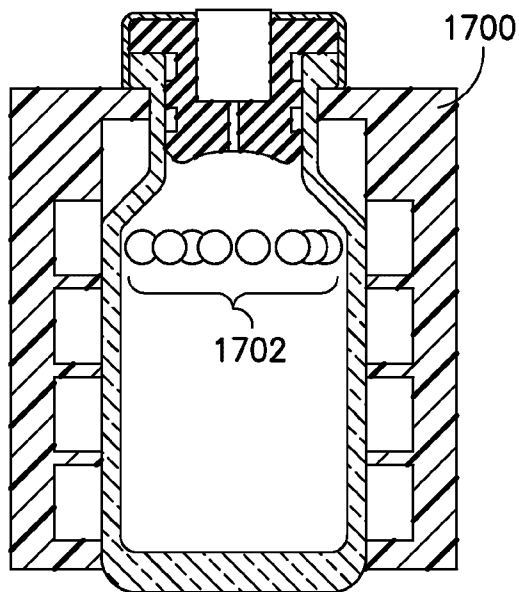


FIG. 17

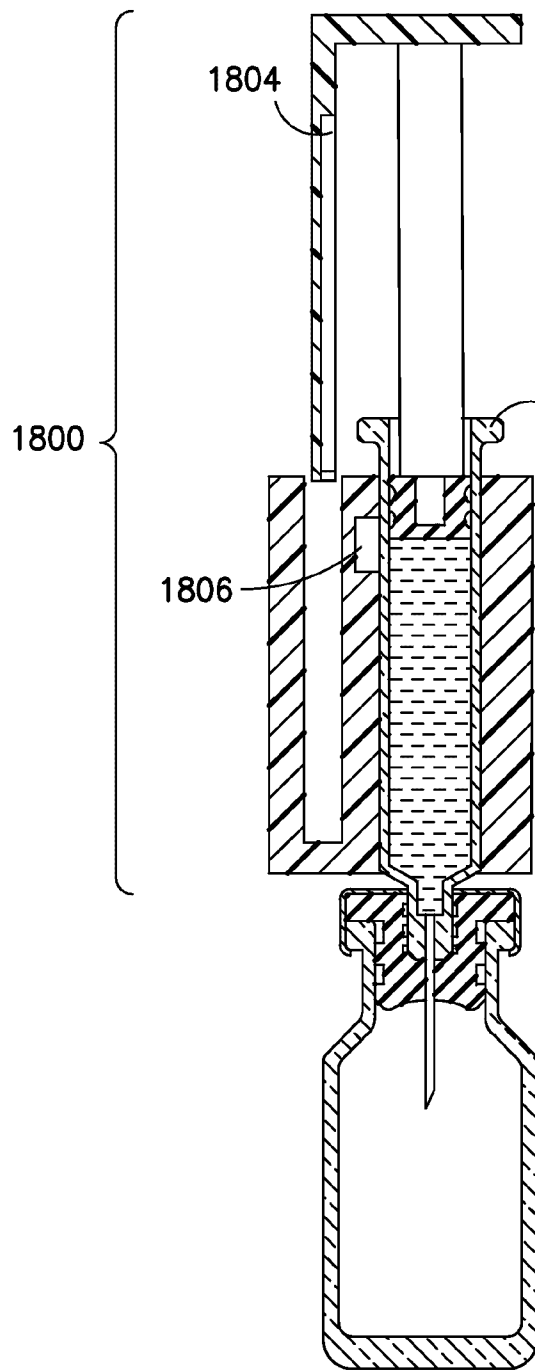


FIG. 18A

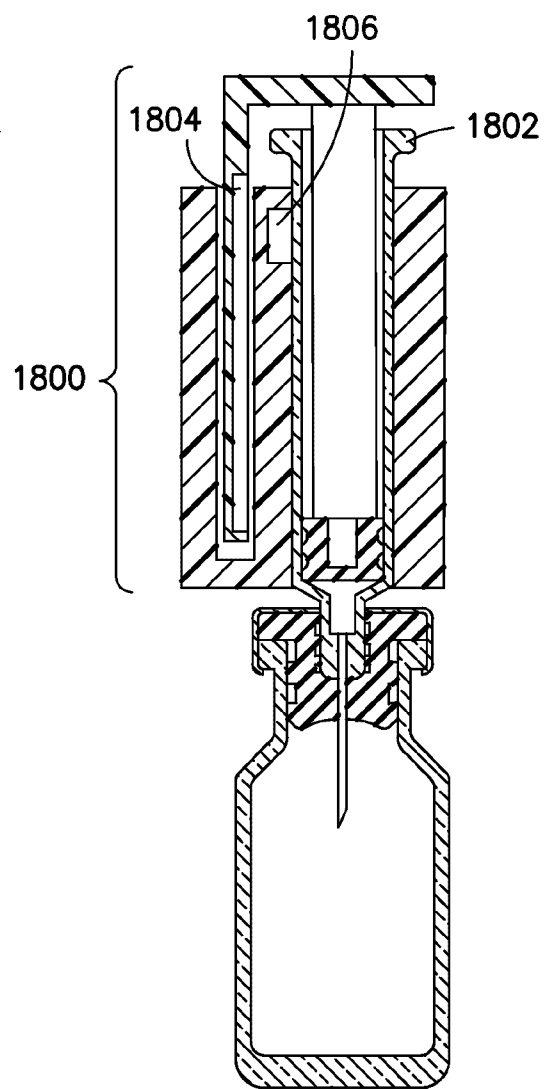


FIG. 18B

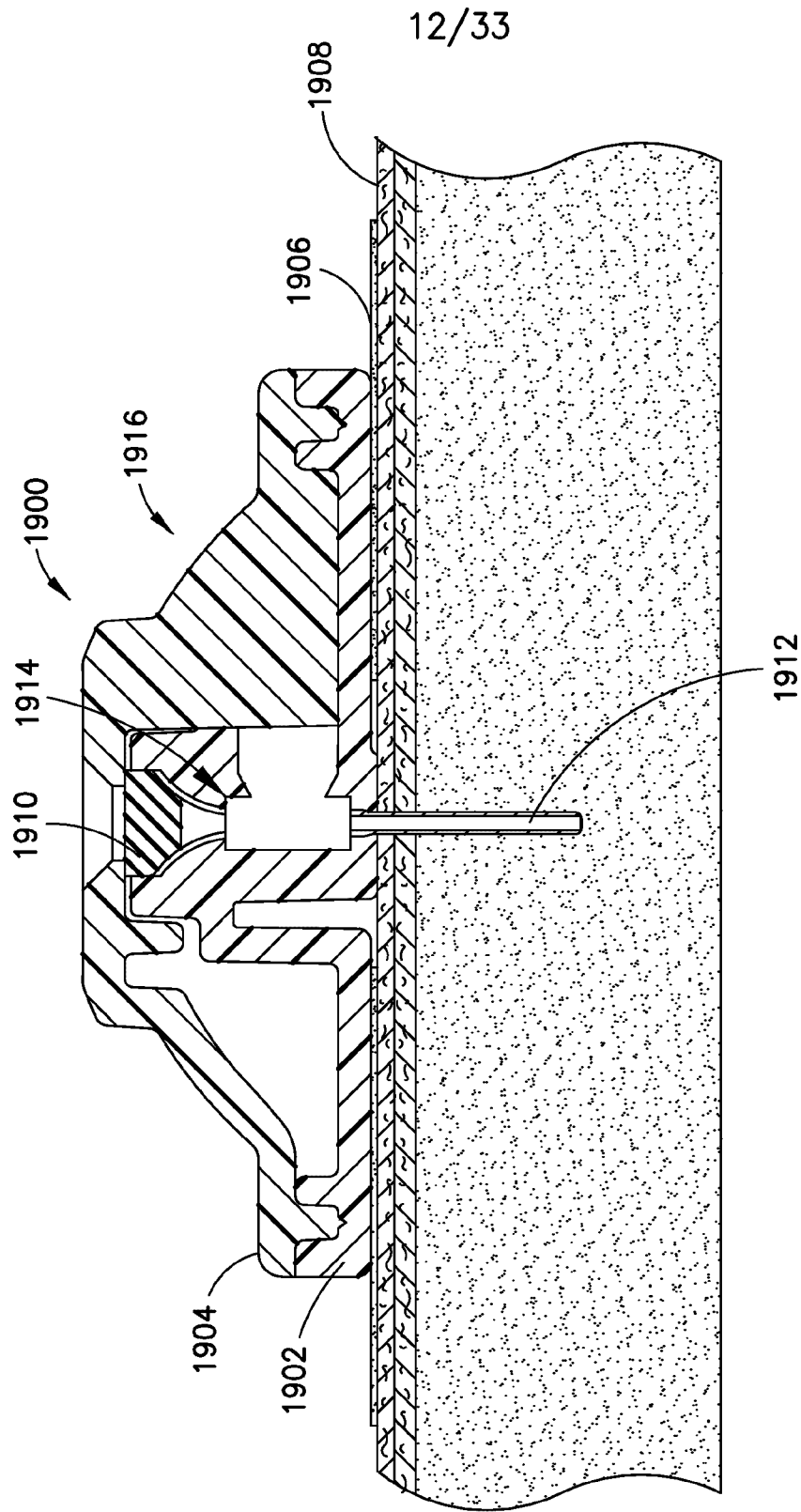


FIG.19A

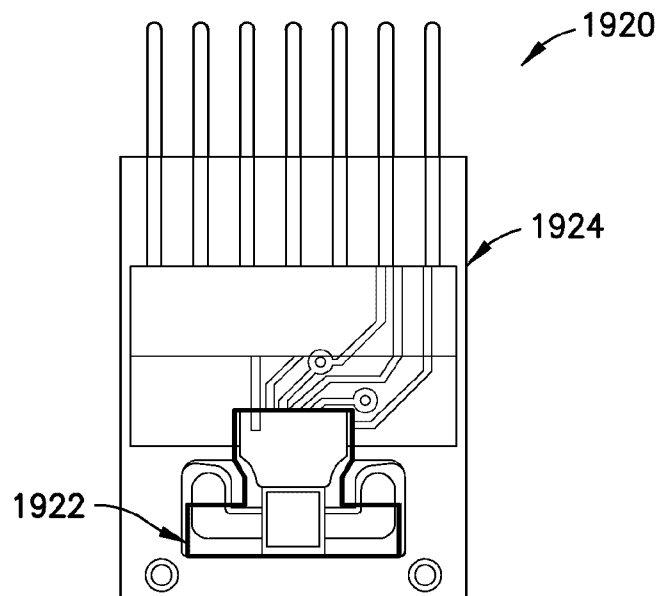


FIG. 19B

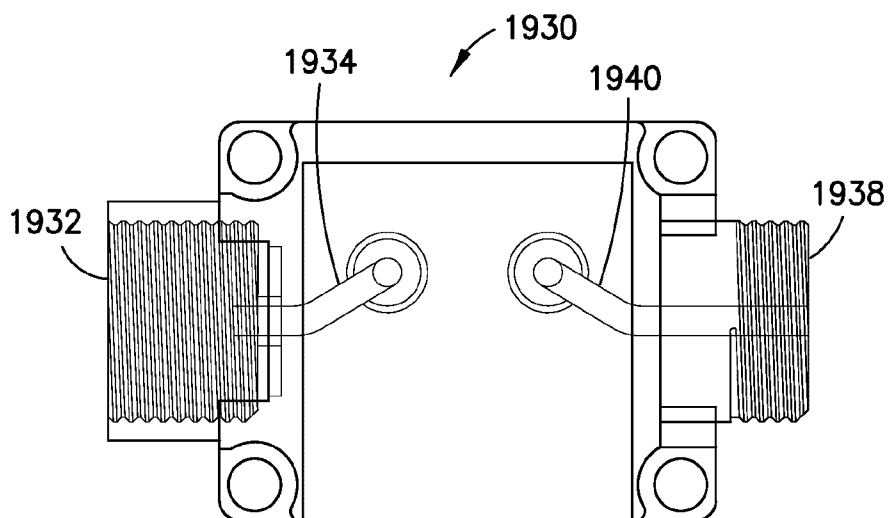


FIG. 19C

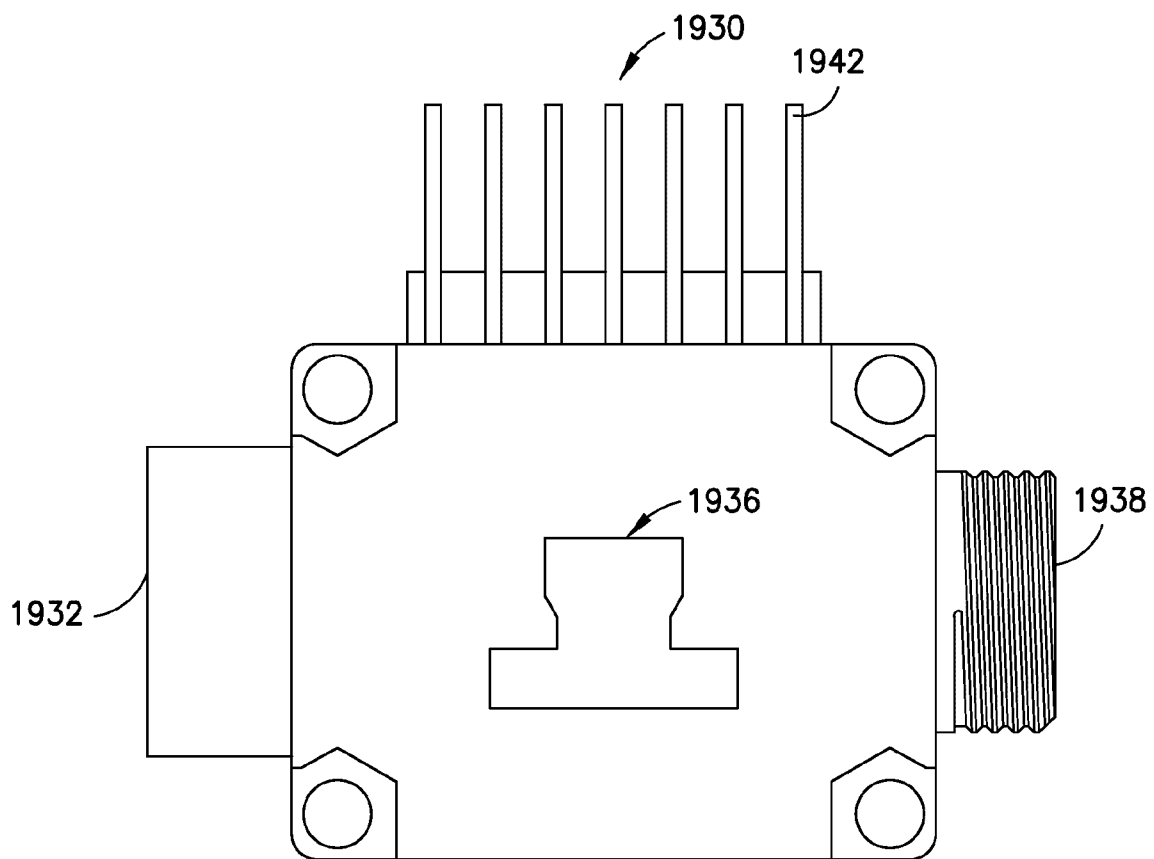


FIG. 19D

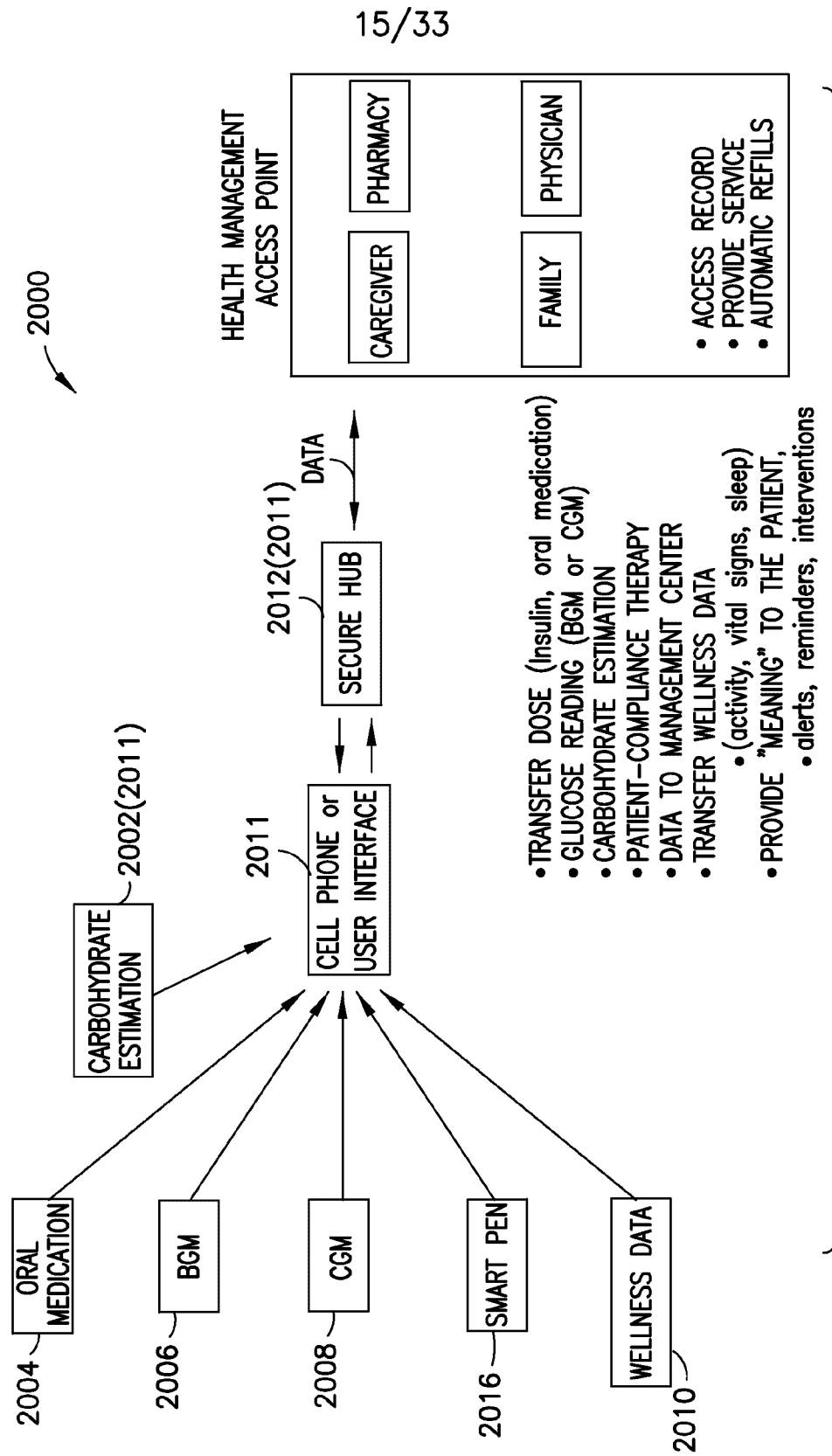
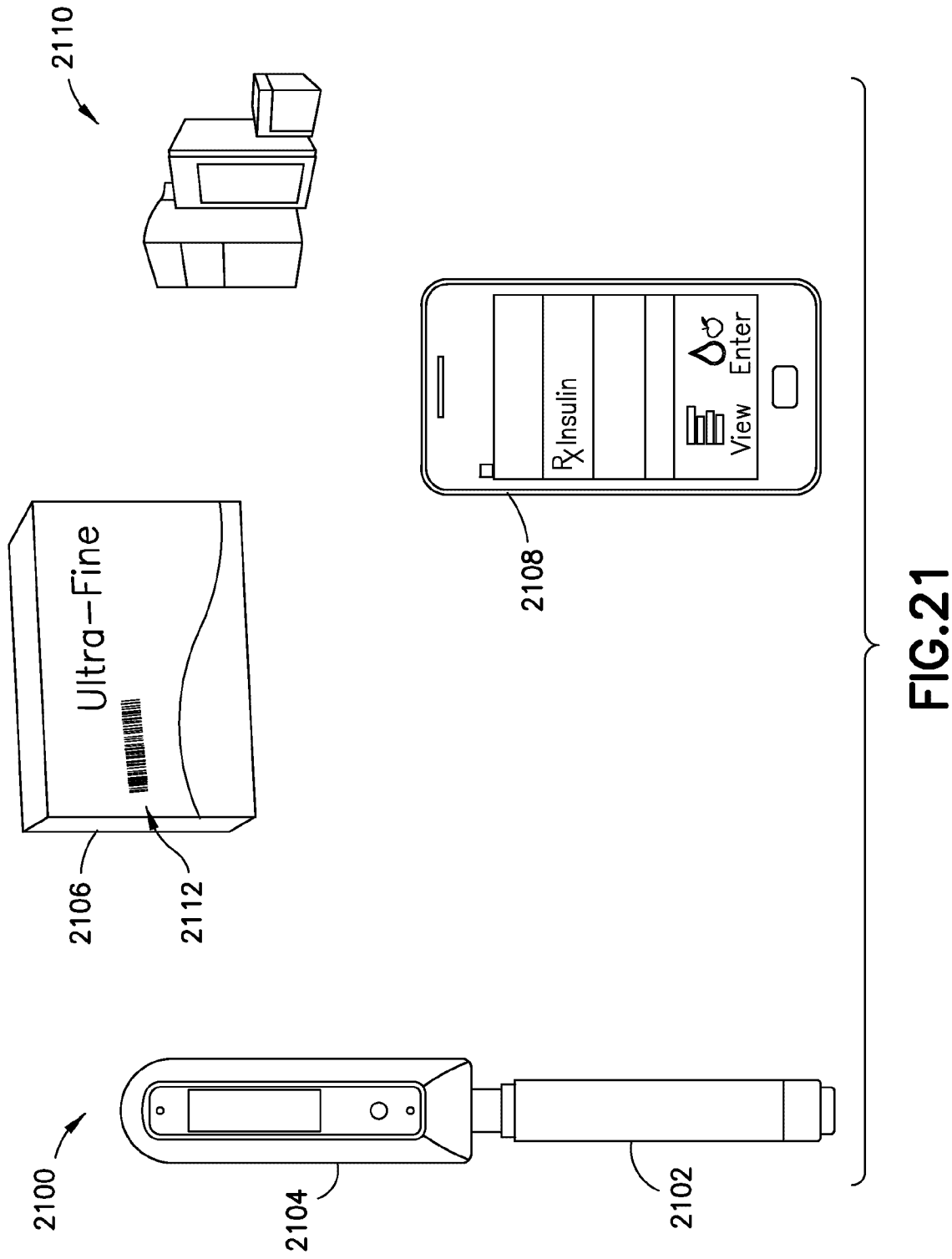


FIG.20



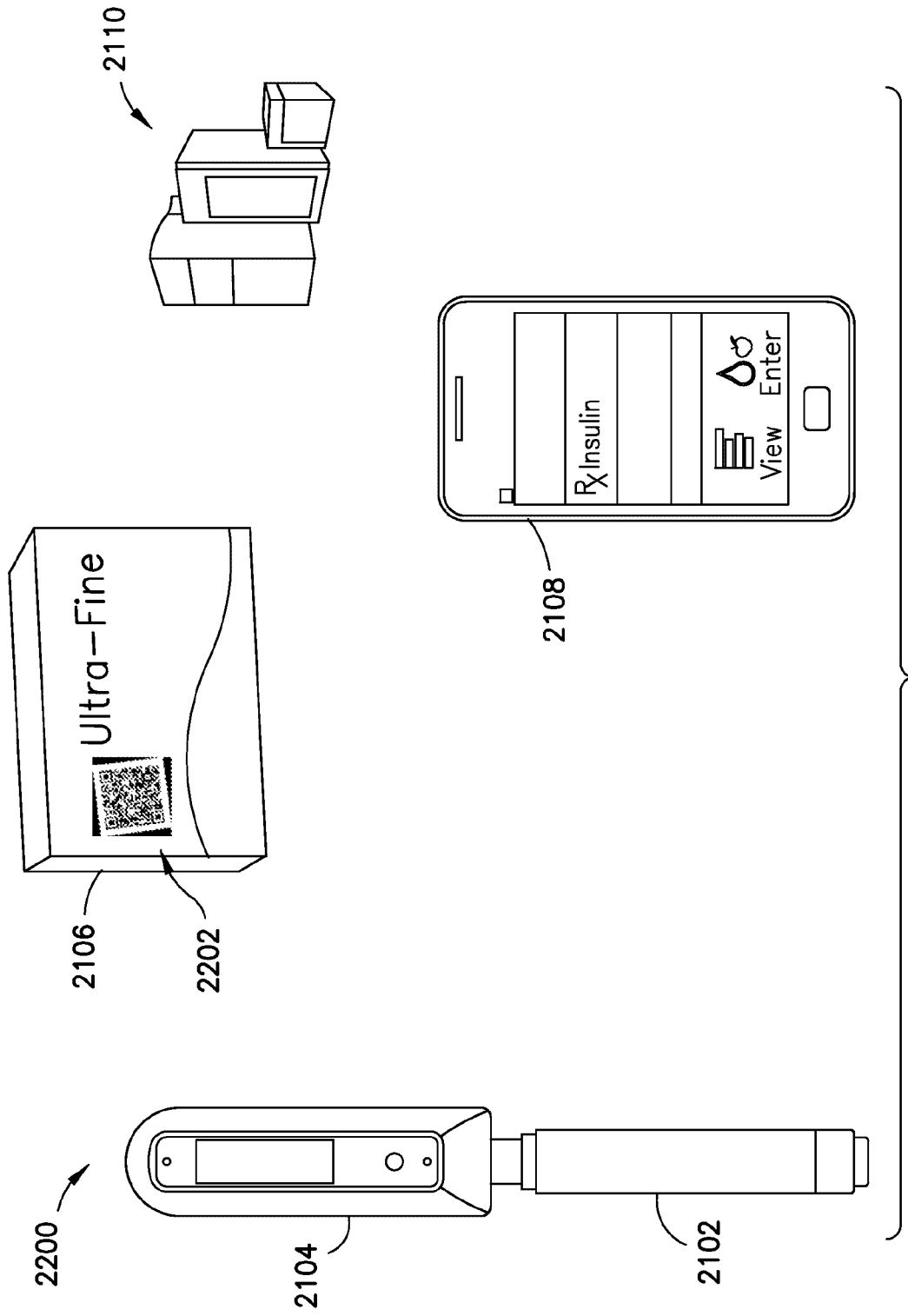
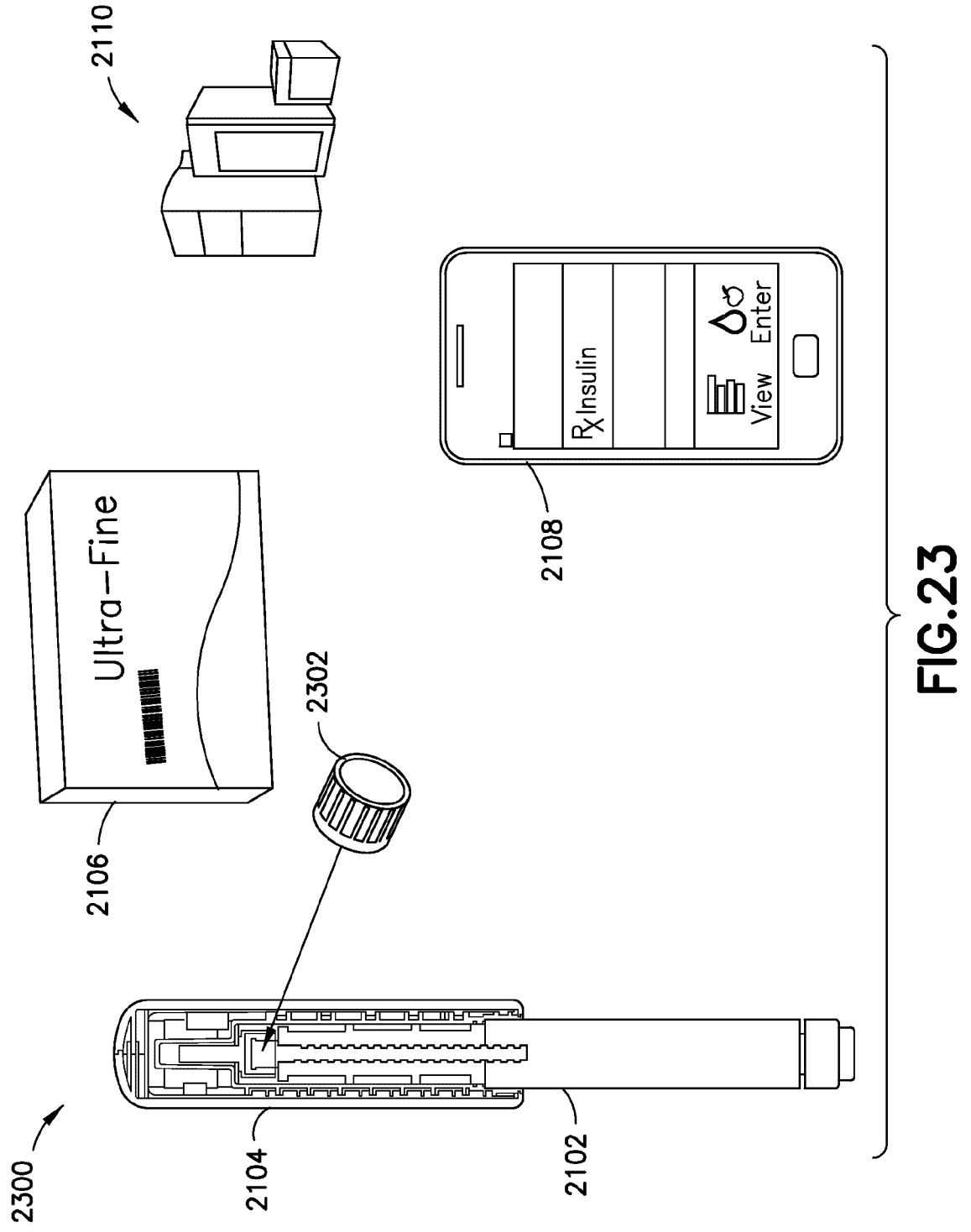
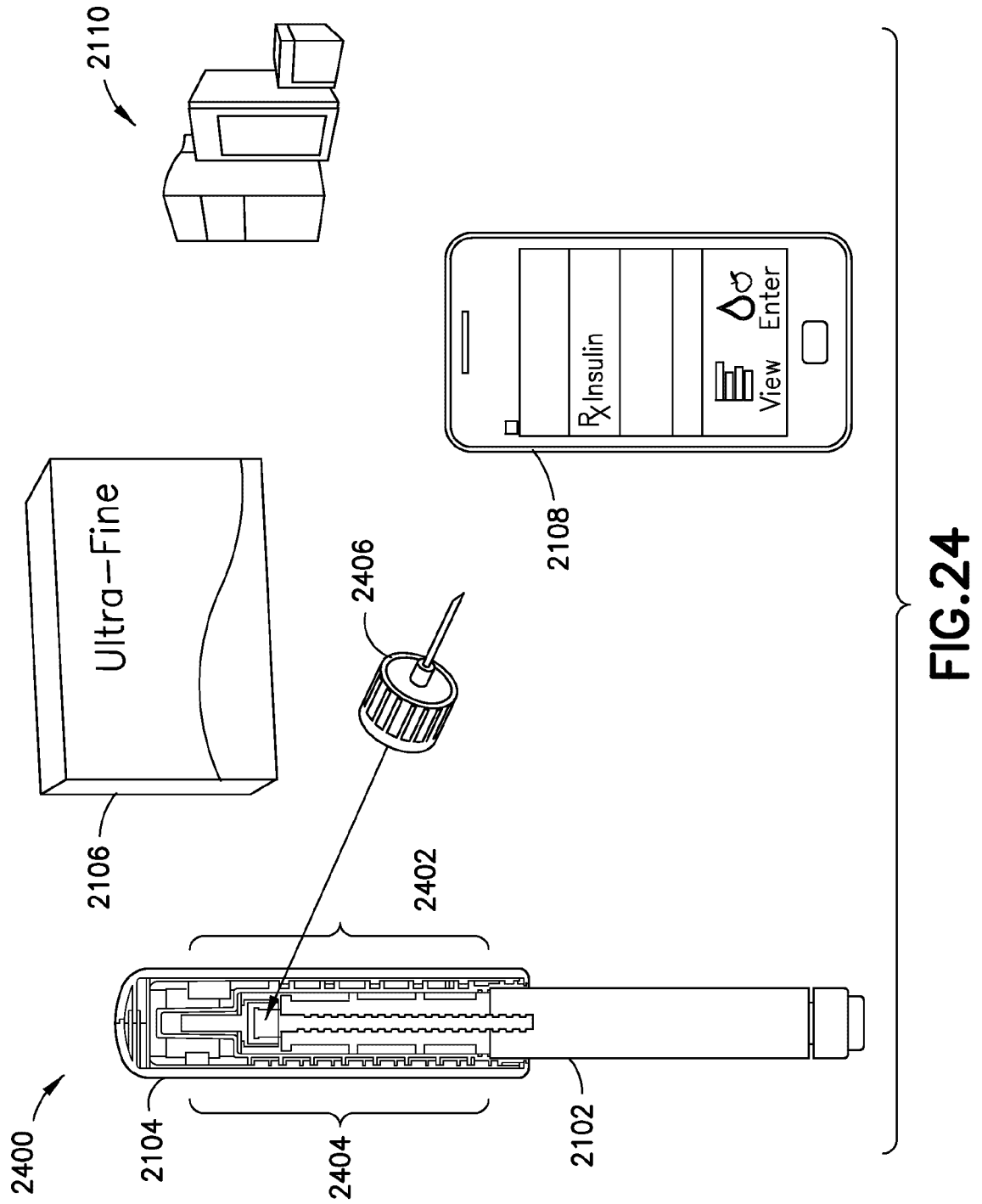


FIG. 22





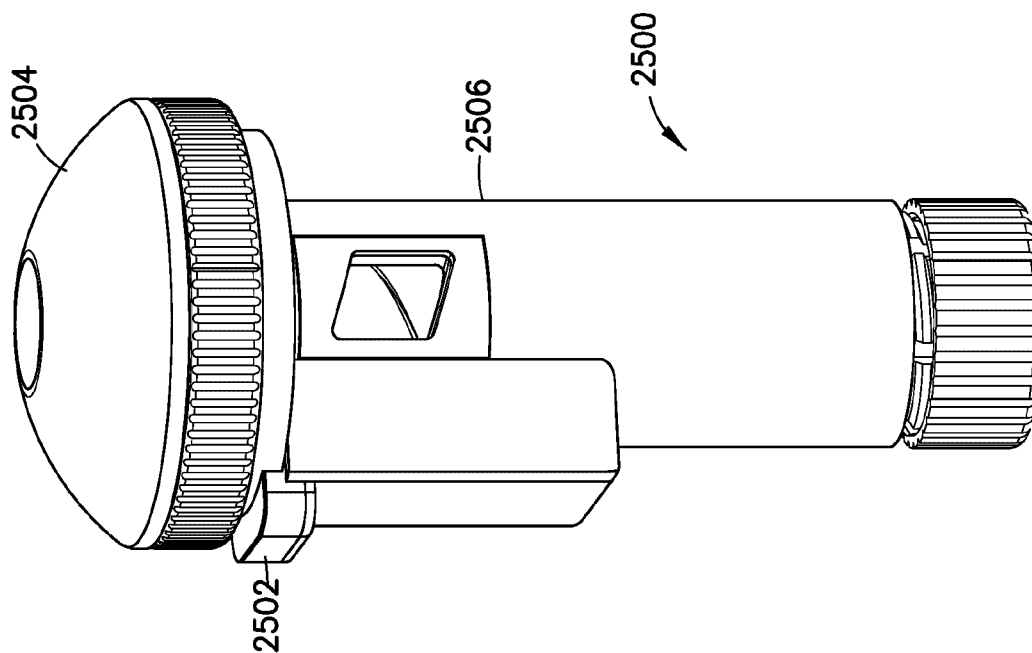


FIG. 26

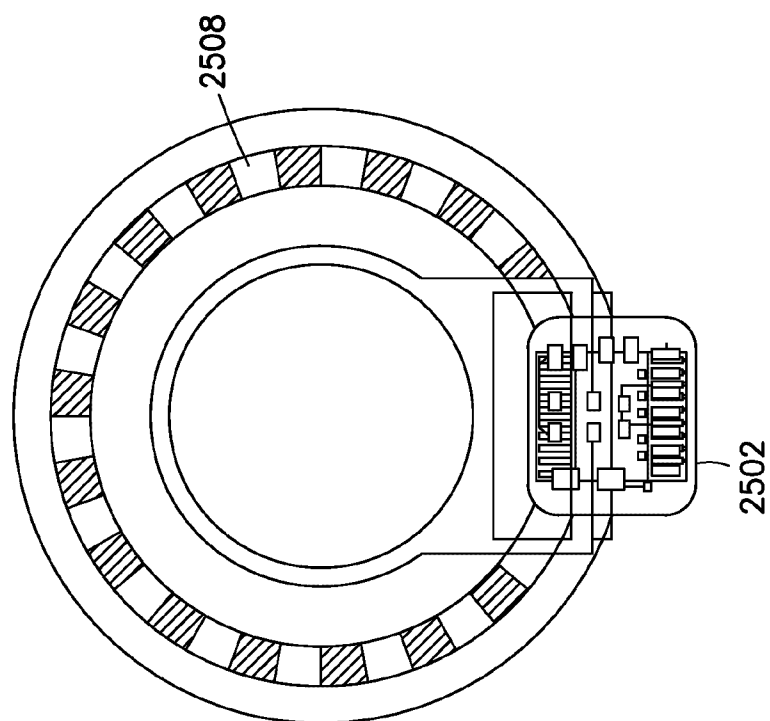


FIG. 25

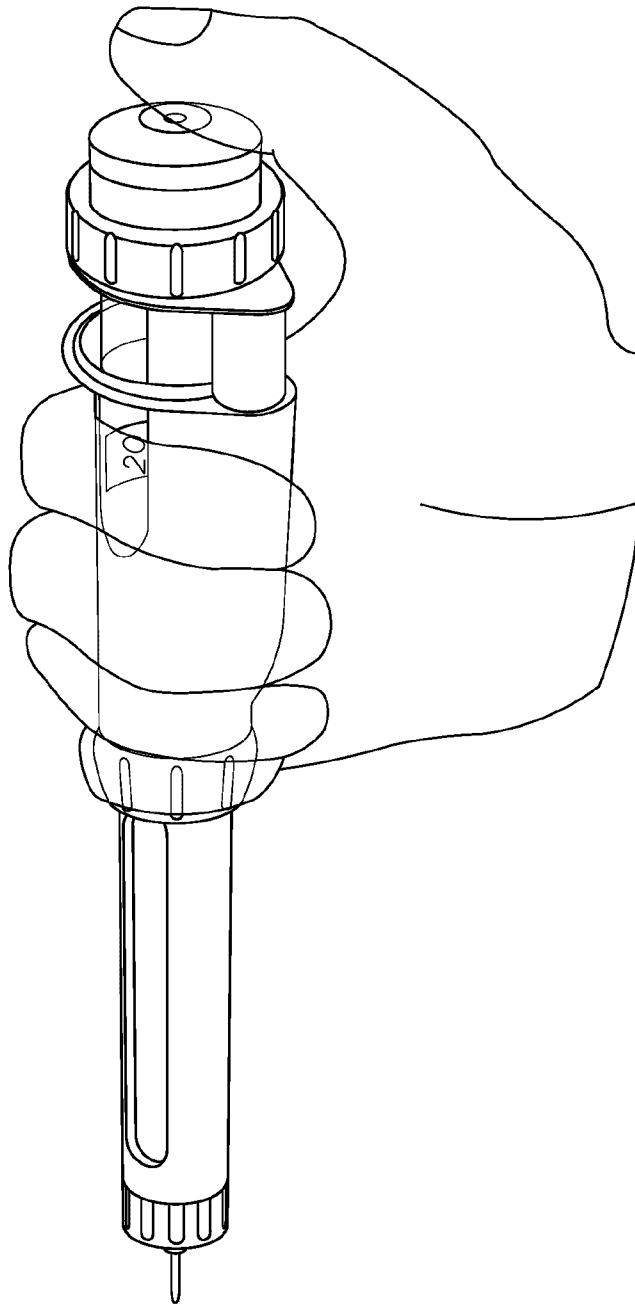


FIG.27

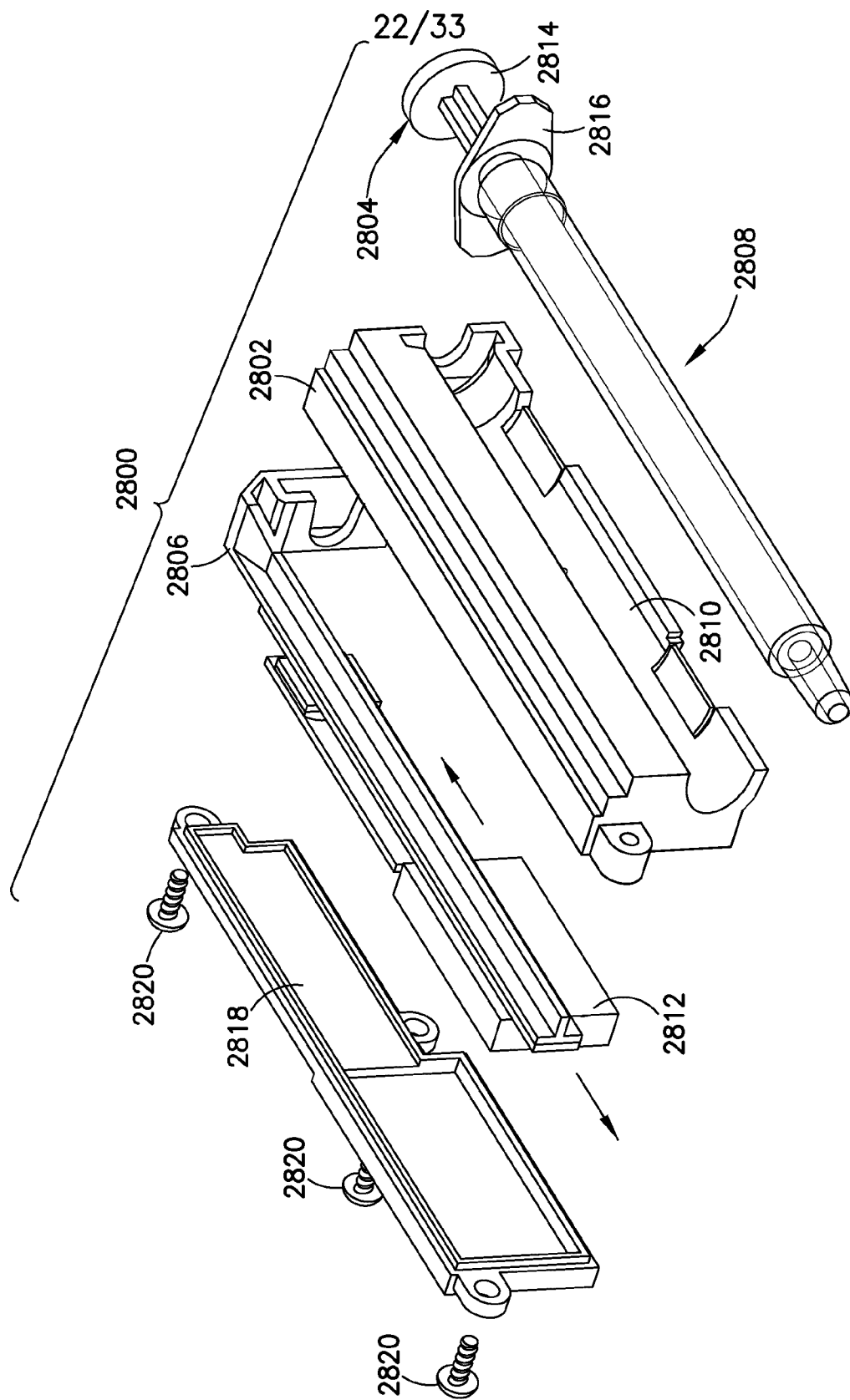


FIG.28

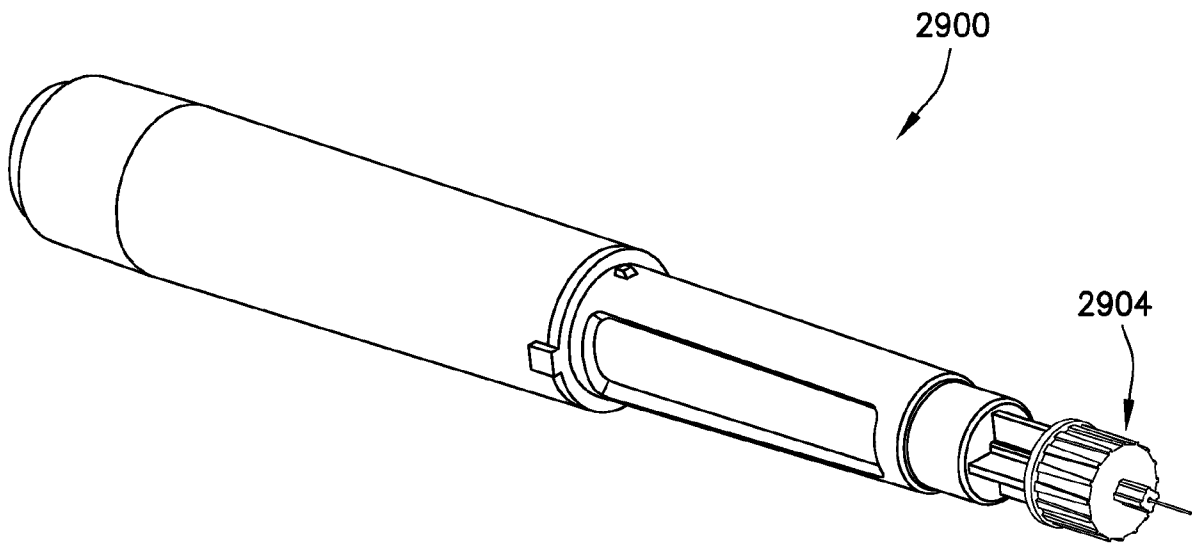


FIG.29

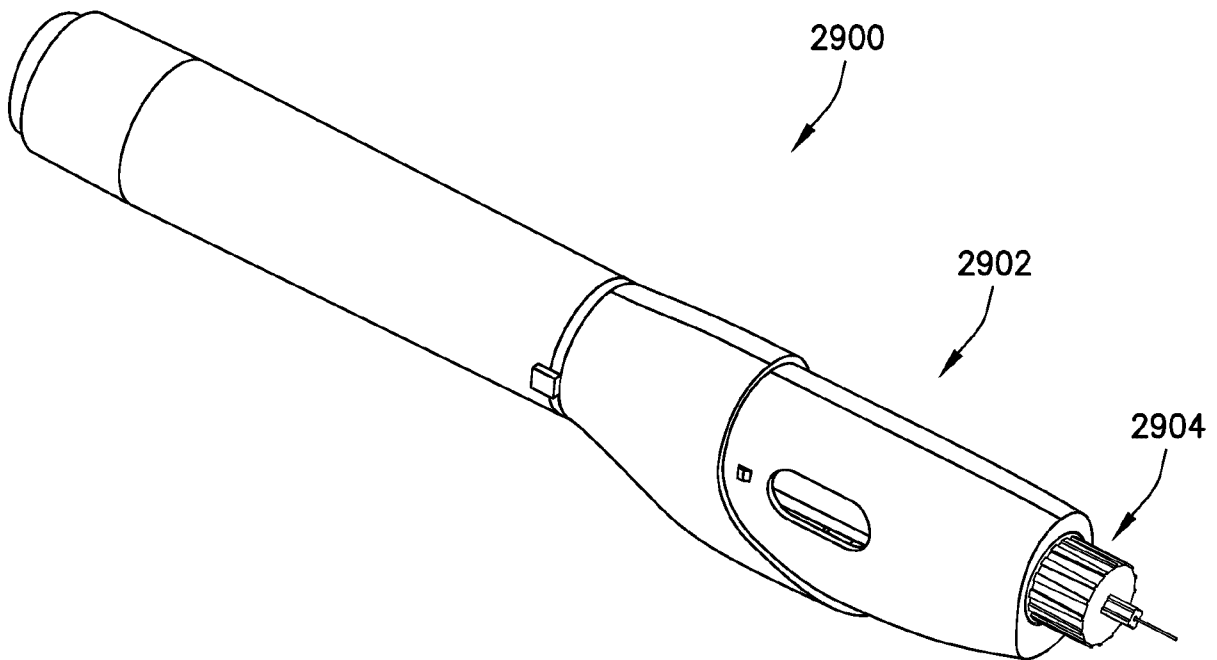


FIG.30

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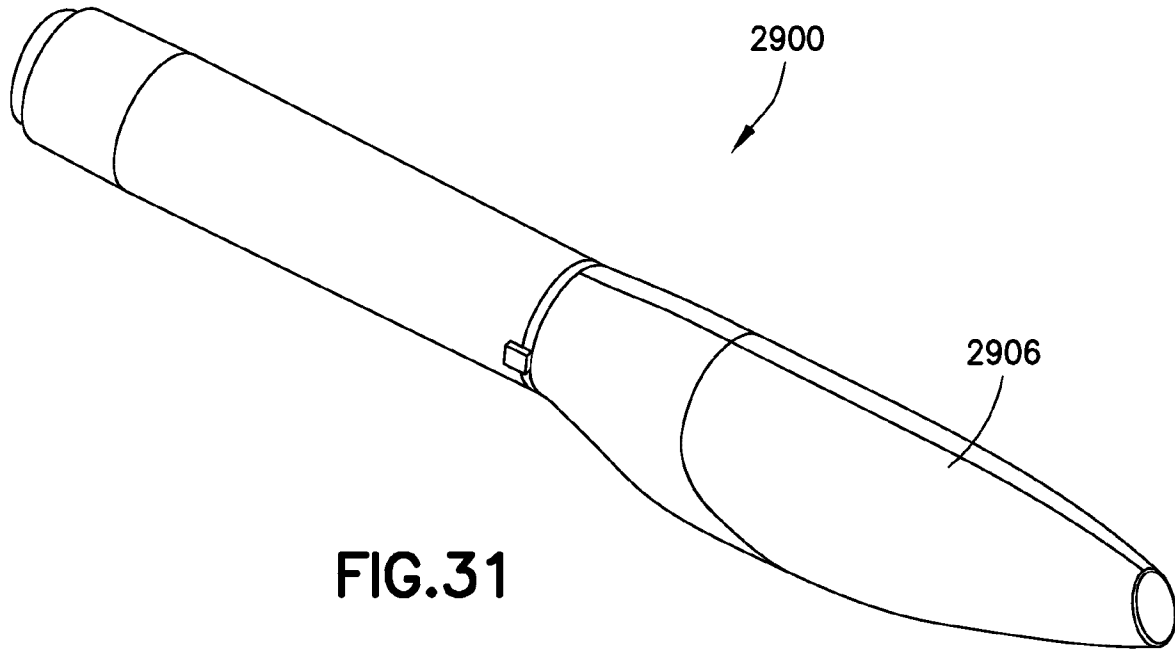


FIG.31

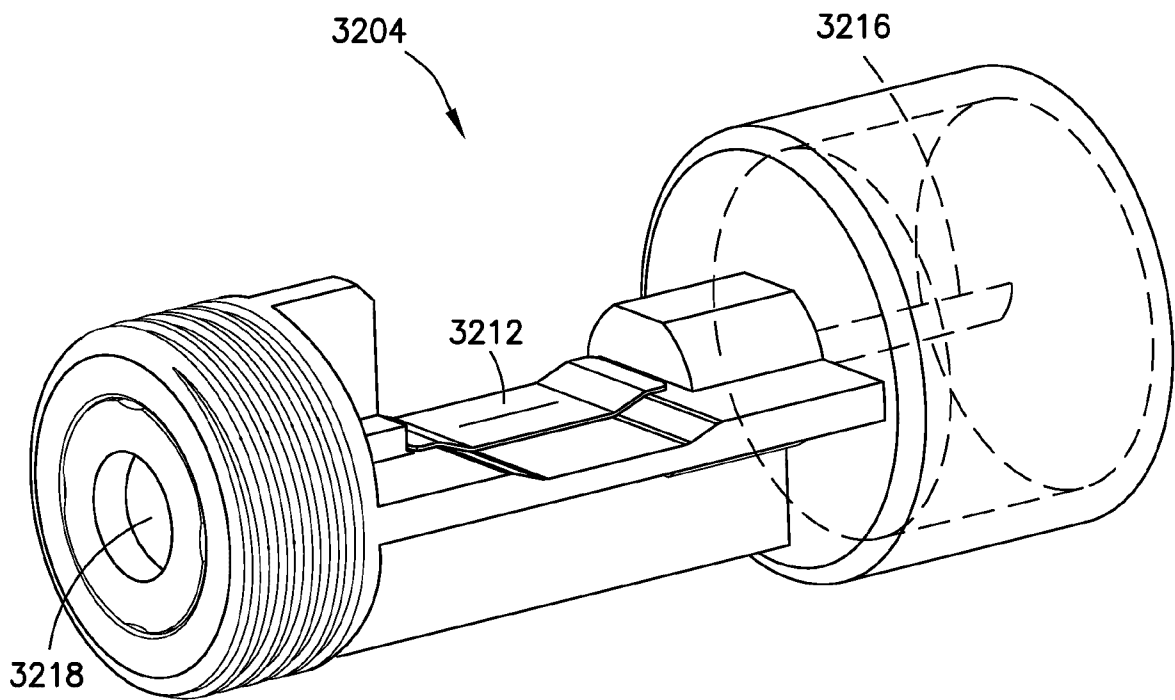


FIG.33

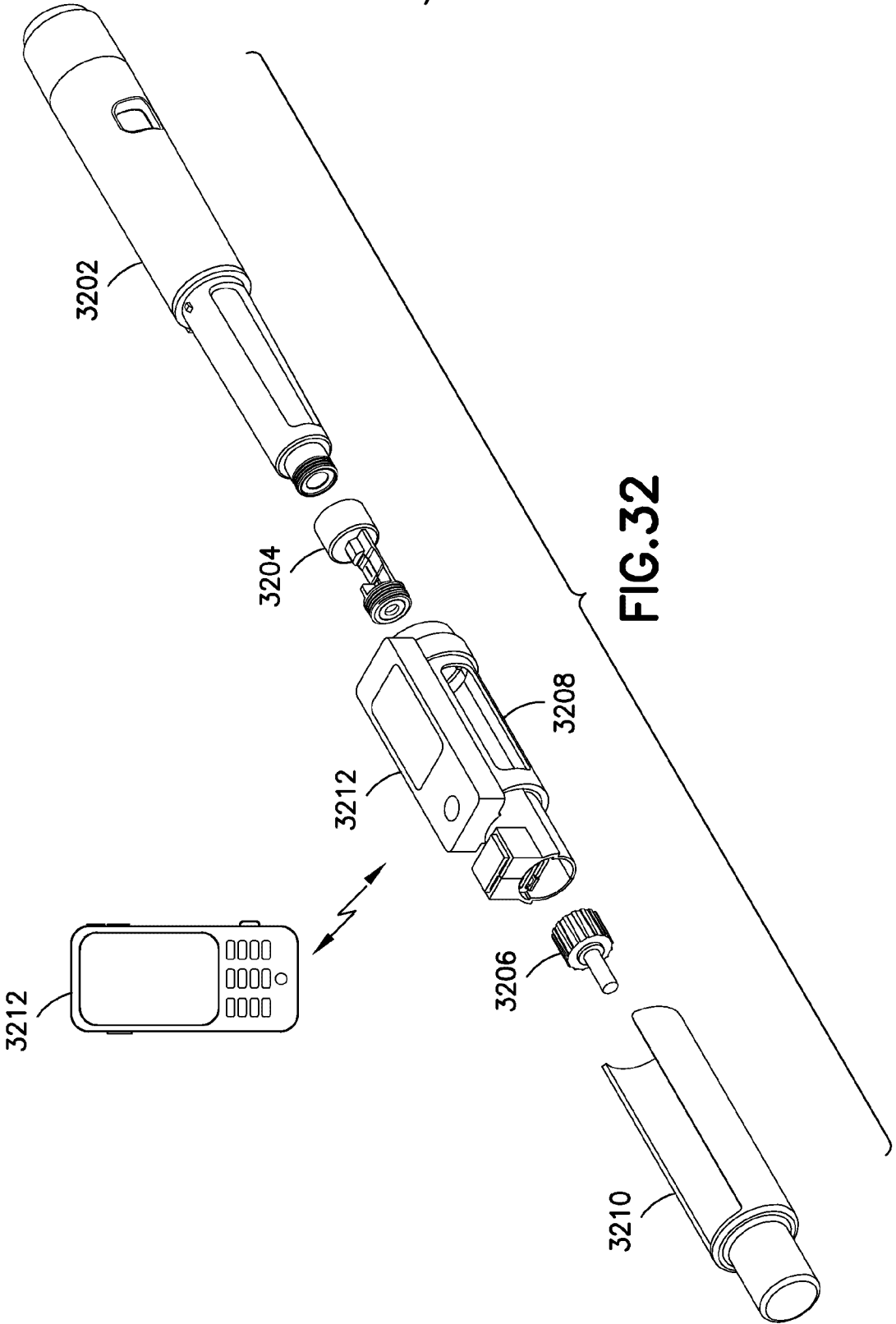
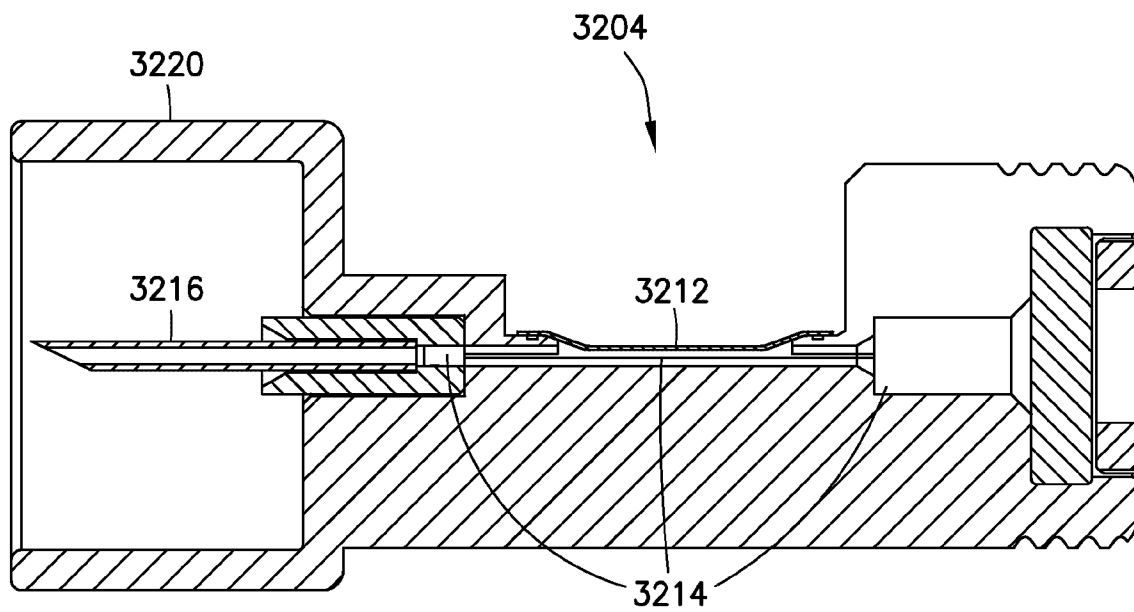
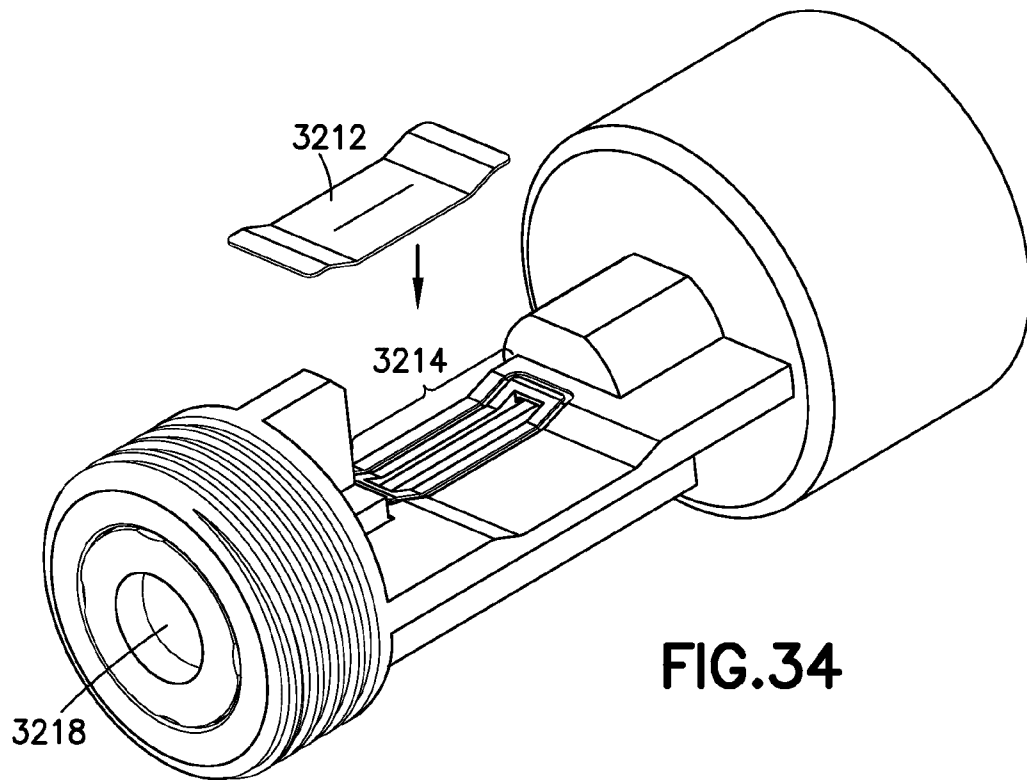


FIG. 32



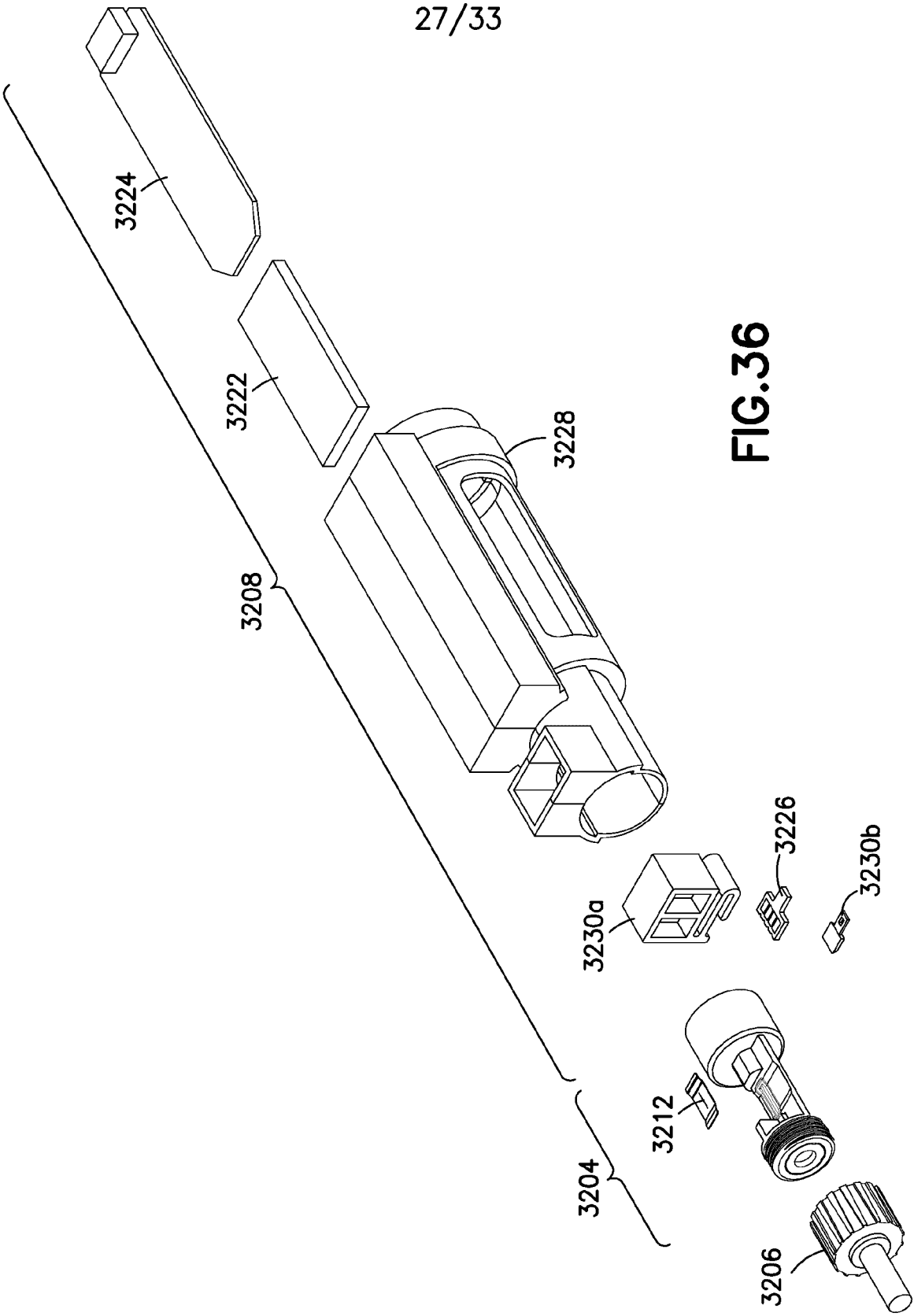
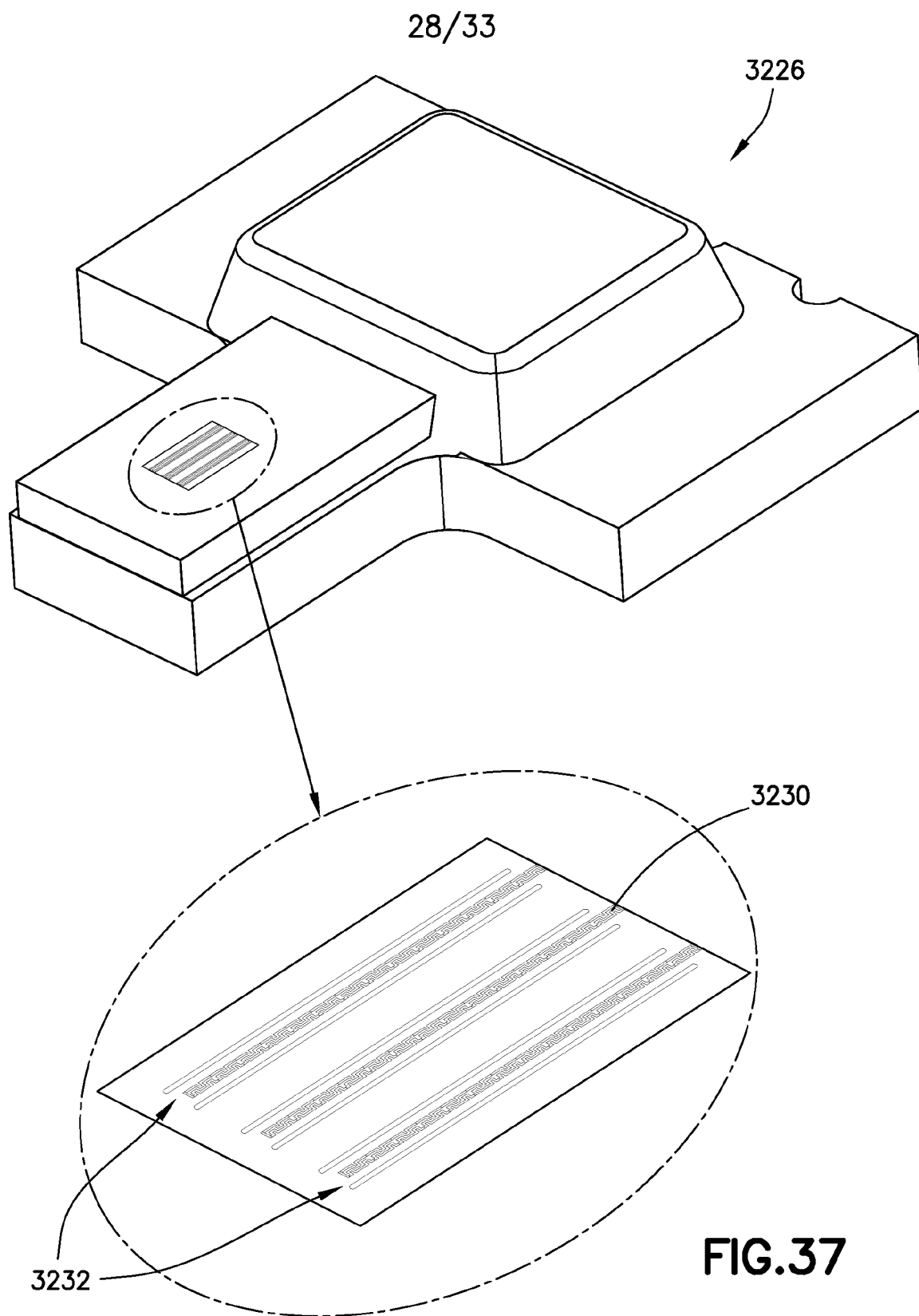


FIG.36



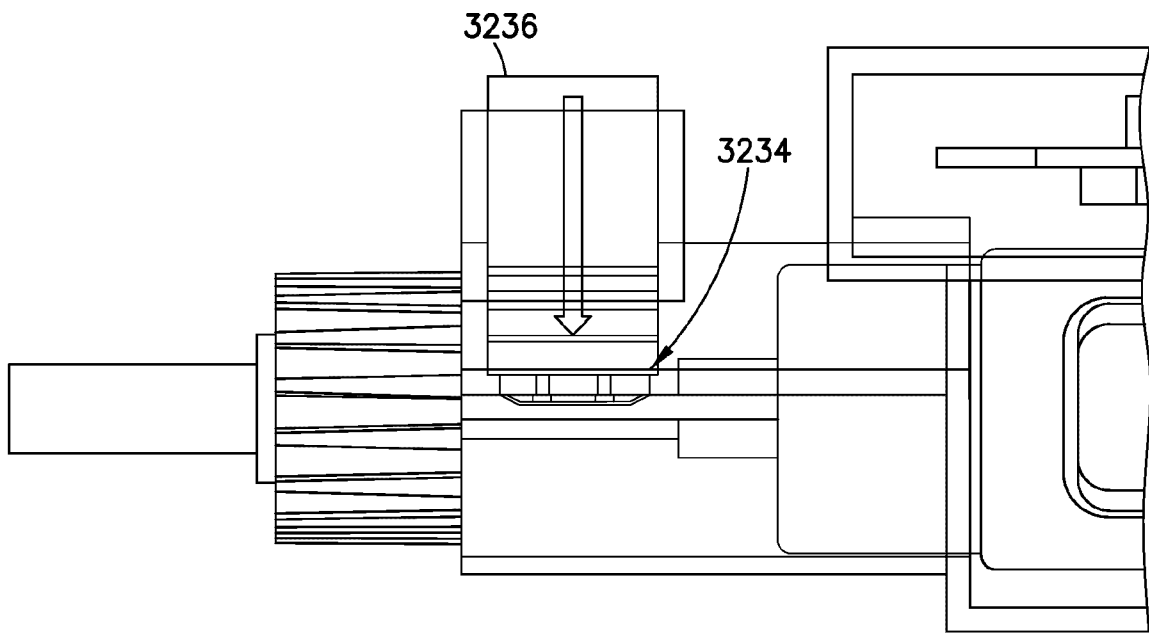


FIG.38

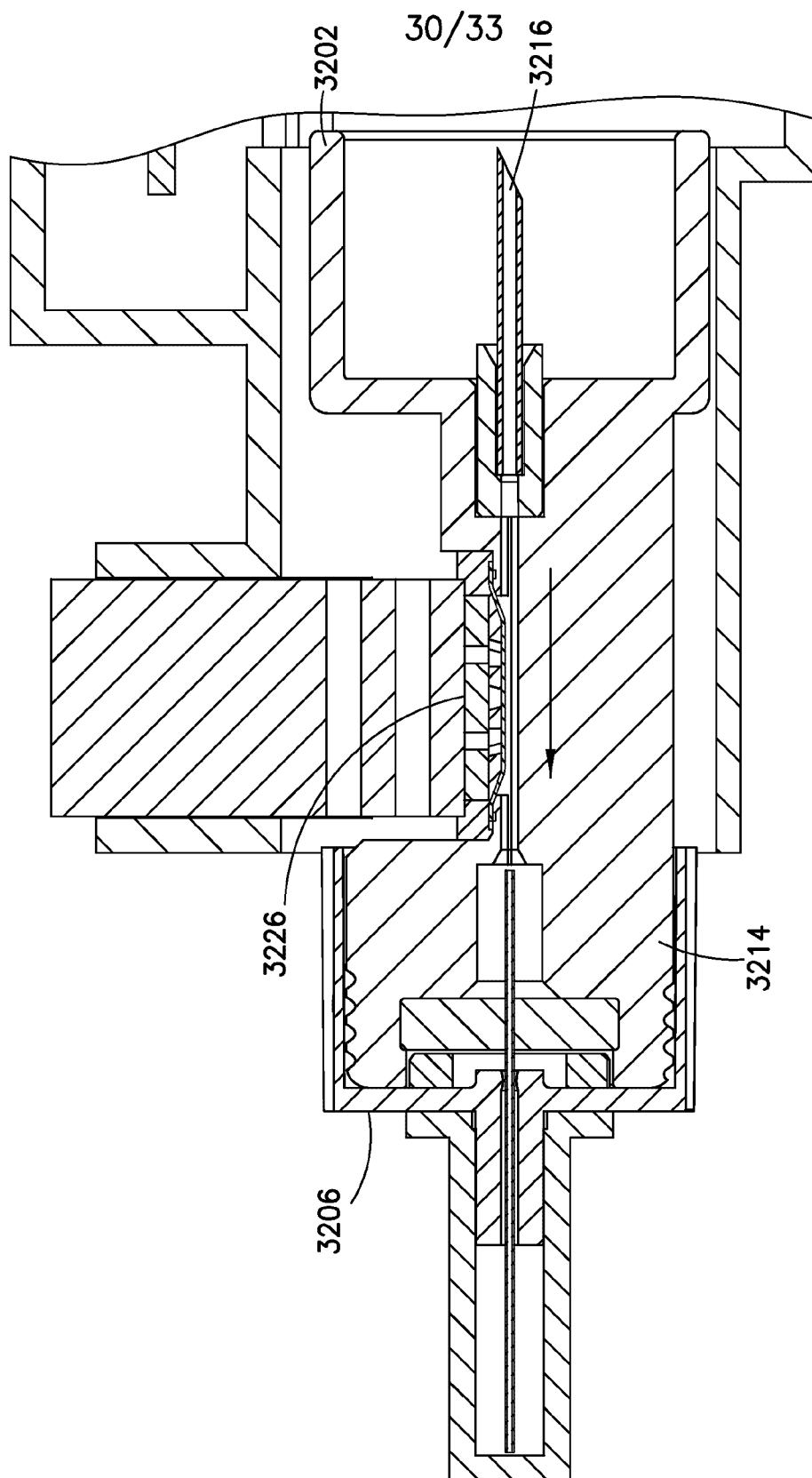


FIG.39

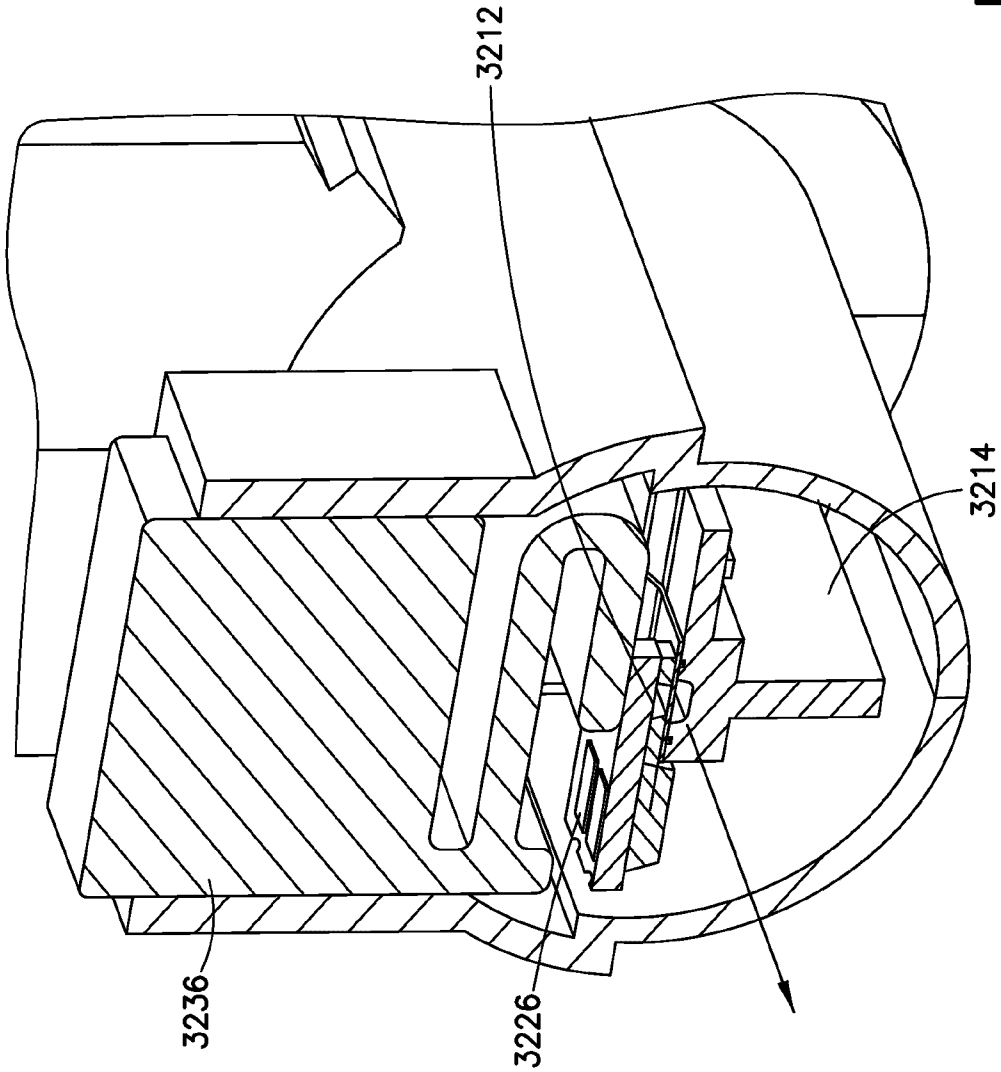
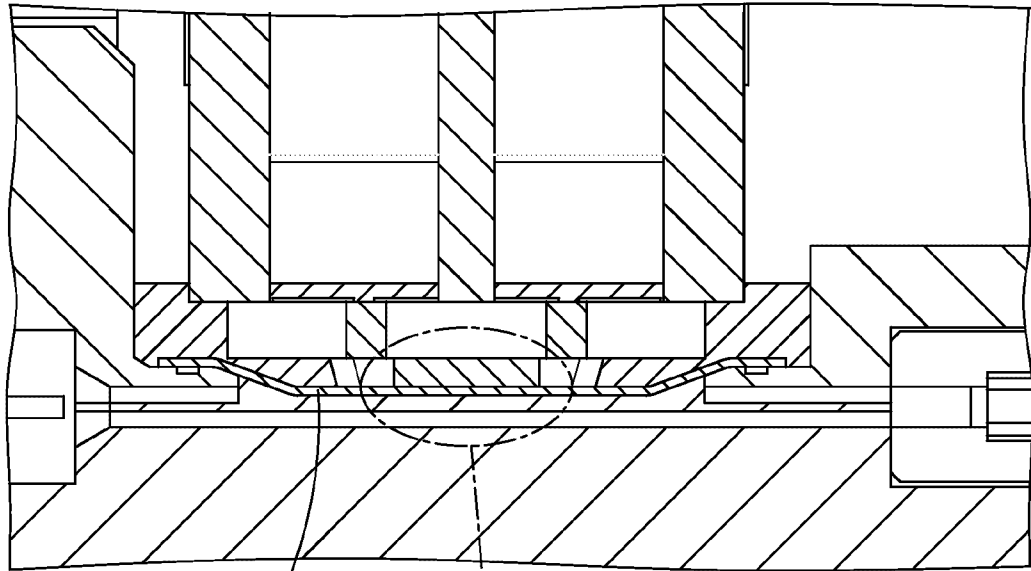


FIG. 40

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3212

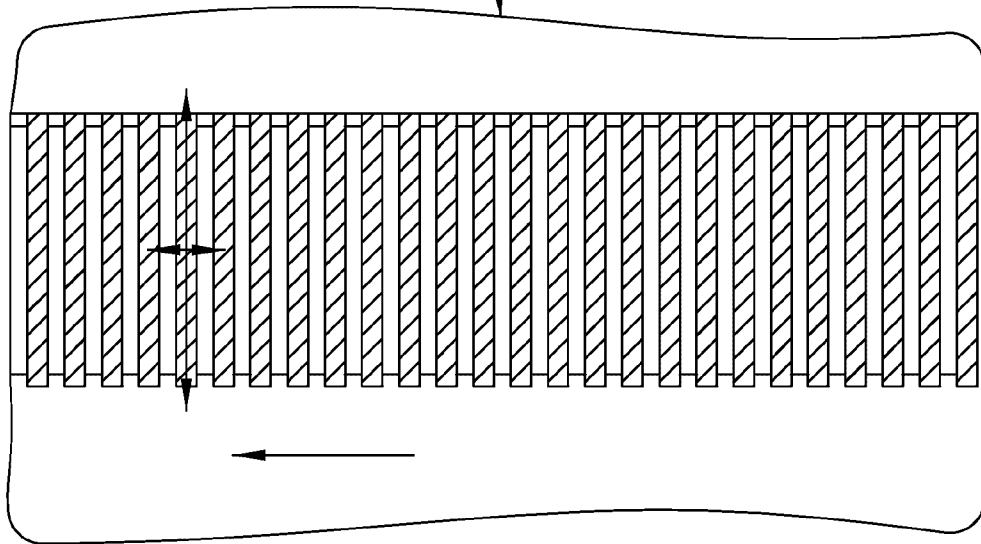


FIG.41

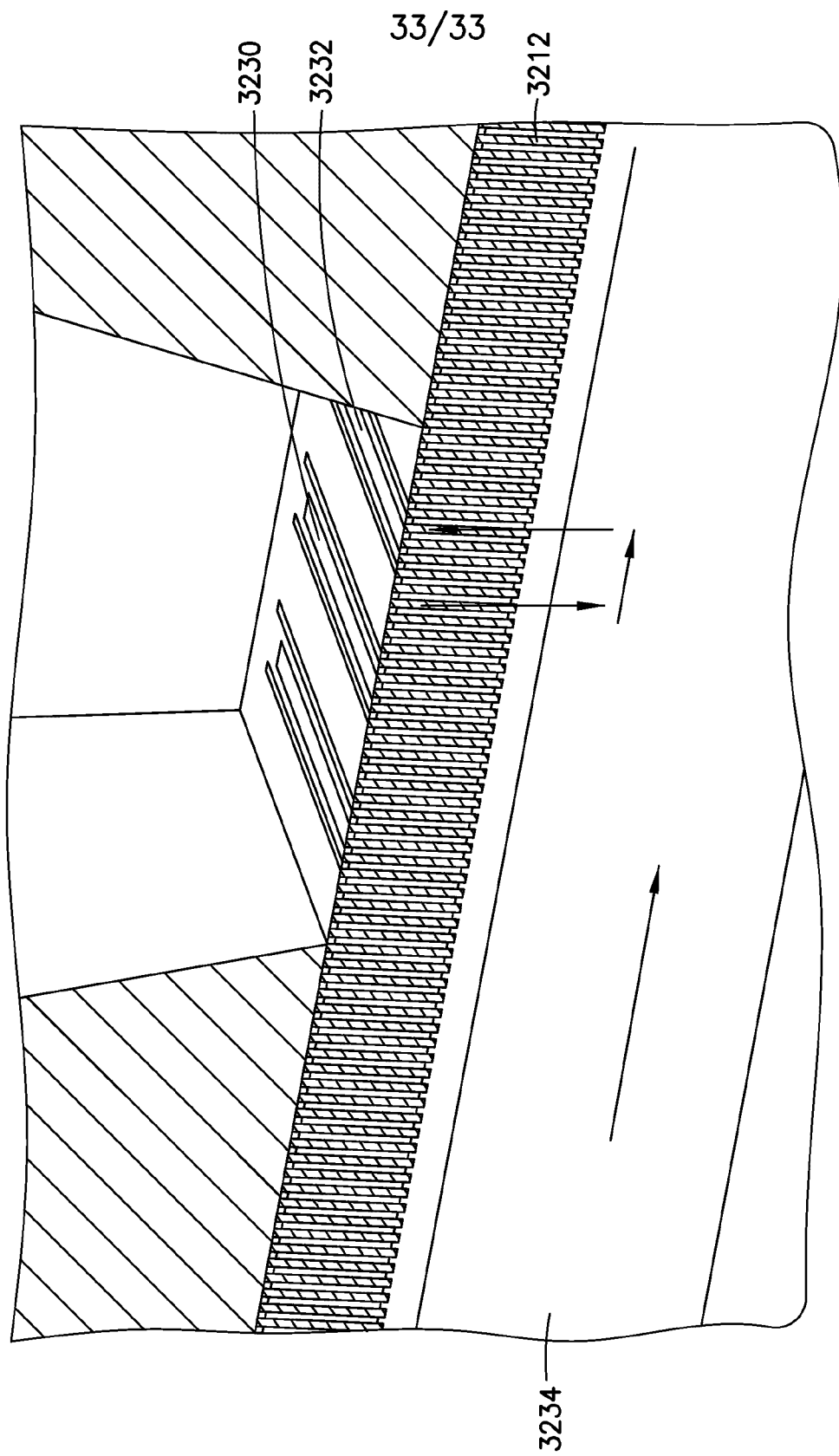


FIG.42