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(54) Title: CARTRIDGE AND SYSTEM FOR ANALYZING BODY LIQUID

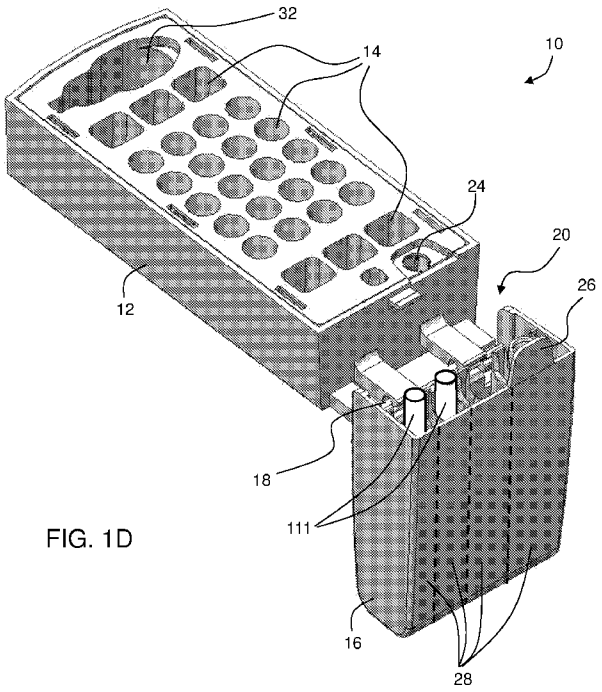

FIG. 1D

(57) Abstract: A cartridge device for analyzing a body liquid comprises a first member having a plurality of wells for performing assays, and a second member having a compartment for holding at least one disposable pipette tip.

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CARTRIDGE AND SYSTEM FOR ANALYZING BODY LIQUID

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

This invention was made with government support under contract number HDTRA1-17-C-0011 awarded by the Defense Threat Reduction Agency and grant number W81XWH-17-1-0694 awarded by the U.S. Army Medical Research Acquisition Activity. The government has certain rights in the invention.

RELATED APPLICATIONS

This application claims the benefit of priority of U.S. Provisional Patent Application Nos. 62/580,496 filed November 2, 2017, 62/581,728 filed November 5, 2017, and 62/694,083 filed July 5, 2018, the contents of which are incorporated herein by reference in their entirety

FIELD AND BACKGROUND OF THE INVENTION

The present invention, in some embodiments thereof, relates to a medical device and, more particularly, but not exclusively, to a cartridge and system for analyzing a sample of body liquid, such as, but not limited to, blood.

The discovery of a vast number of disease biomarkers and the establishment of miniaturized medical systems facilitates the prediction, diagnosis and/or monitoring of treatment of diseases in a point-of-care (POC) setting. Point-of-care systems can rapidly deliver test results to medical personnel, other medical professionals and patients. Early diagnosis of a disease or disease progression can allow medical personnel to begin or modify therapy in a timely manner.

Multiplexed biomarker measurement can provide additional knowledge of the condition of a patient. For example, when monitoring the effects of a drug, three or more biomarkers can be measured in parallel. Typically, microtiter plates and other similar apparatuses have been used to perform multiplexed separation-based assays. A microtiter plate can perform a large number of assays in parallel.

U.S. Patent No. 8,409,872 discloses a cartridge having two or more lines of well groups arranged in parallel, wherein each well group comprises a diluting well, and a reaction well in which a component in the sample reacts with a substance. A diluting solution is filled in the diluting well of each well group, and the cartridge is then sealed. The cartridge seal is pierced and the sample is dispensed in the diluting well of each well group to dilute the sample. The

component in the diluted sample is reacted with the substance, and the amount of the reaction product is measured.

Additional background art includes U.S. Published Application Nos. 20130287651 and 20140017712, and U.S. Patent Nos. 7,157,047, 7,473,396, 8,142,737, 8,211,386, 8,333,930, 8,383,421, 8,476,080, 8,697,377, 9,335,339, 9,446,406.

SUMMARY OF THE INVENTION

According to an aspect of some embodiments of the present invention there is provided a cartridge device for analyzing a liquid, such as, but not limited to, a body liquid. The cartridge comprises a first member having a plurality of wells for performing assays; and a second member, connected to the first member, and having a compartment for holding at least one disposable pipette tip in a generally upright orientation.

While the embodiments below are described with a particular emphasis to body liquid, it is to be understood that the device, kit, system and method described herein can be also employed in some embodiments of the present invention for analyzing other types of liquids, such as, but not limited to, liquid from river, sewage, water reservoir, food product and the like.

According to some embodiments of the invention the second member is hingedly connected to the first member.

According to some embodiments of the invention the second member is slideably connected to the first member.

Optionally, the first and second members are not connected to each other and are loaded separately into a system that analyzes the liquid.

According to some embodiments of the invention the second member is oriented for holding the disposable pipette tip(s) in a generally upright orientation.

According to an aspect of some embodiments of the present invention there is provided a kit for analyzing a liquid (*e.g.*, body liquid). The kit comprises a first member having a plurality of wells for performing assays; and a second member, connectable to the first member, and having a compartment for holding at least one disposable pipette tip.

According to an aspect of some embodiments of the present invention there is provided a cartridge device for analyzing liquid (*e.g.*, body liquid). The cartridge device comprises a first plurality of wells, each having a tapered base; and a second plurality of wells. The two pluralities of wells are formed in a monolithic structure. At least some of the wells of the first plurality of wells contain a reagent therein. In some embodiments of the present invention one or more of the wells of the first plurality of wells is empty. One or more of the wells of the second plurality of

wells is empty. In use, one or more of the empty wells of the second plurality of wells is optionally and preferably filed with a liquid to be analyzed, such as, but not limited to, a body liquid. Optionally, one or more of the wells of the second plurality of wells contain a reagent therein.

According to some embodiments of the invention the device comprises a covering structure covering the wells, the covering structure being selected from the group consisting of a pierceable foil, a non-flexible openable lid, a flexible openable lid, a one way valve, a labyrinth structure.

According to some embodiments of the invention some of the wells are open and are not covered by a foil.

According to some embodiments of the invention the bottom of at least some the wells are shaped in a general conic shape.

According to some embodiments of the invention the bottom of at least some the wells are shaped in a generally spheric, round shape.

According to some embodiments of the bottom shape of the wells is spheric-round for some of the wells and conic for some other wells.

According to some embodiments of the invention the device comprises a waste collecting chamber.

According to some embodiments of the invention the waste collecting chamber is covered by a structure selected from the group consisting of a pierceable foil, a non-flexible openable lid, a flexible openable lid, and a one way valve.

According to some embodiments of the invention the waste collecting chamber comprises a moisture absorber.

According to some embodiments of the invention the waste collecting chamber is covered by a lid connected to or being an extension of the second member, to be exposed when the second member is hinged in a generally upright orientation.

According to some embodiments of the invention the waste collecting chamber is covered by a foil, which is pierced to expose a waste collecting chamber before deposing waste to it.

According to some embodiments of the invention the waste collecting chamber is comprised of multiple chambers, each is a single use chamber, to which there is a single deposing of waste.

According to some embodiments of the invention, the waste collecting chamber is comprised on one chamber, with several entrance points.

According to some embodiments of the invention the waste collecting chamber sealing foil is capable of being pierced several times in the same location

According to some embodiments of the invention the waste collecting chamber sealing foil is covered by a label.

According to some embodiments of the invention the waste collecting chamber covering label is scored along a pattern to form a frangible piercing location defined by the pattern.

According to some embodiments of the invention there is a plurality of frangible piercing locations, defined by a respective plurality of scored patterns.

According to some embodiments of the invention, at least two adjacent scored patterns are separated from each other. According to some embodiments of the invention, any two adjacent scored patterns are separated from each other

According to some embodiments of the invention, at least one scored pattern has a shape of a cross. According to some embodiments of the invention, the cross is a right angle cross, e.g., shape of a plus symbol. According to some embodiments of the invention, the cross is acute angle cross, e.g., shape of an X symbol.

According to some embodiments of the invention, at least two adjacent scored pattern have shapes of differently oriented crosses or differently shaped crosses, to ensure that said scored patterns are separated from each other.

According to some embodiments of the invention, the scored patterns comprise right angle crosses, e.g., shape of plus symbols, and acute angle crosses, e.g., shape of X symbols, arranged in alternating manner.

According to some embodiments of the invention the waste collecting chamber extends to beneath the wells.

According to some embodiments of the invention the waste collecting chamber is part of the first member.

According to some embodiments of the invention the waste collecting chamber is part of the second member.

According to some embodiments of the invention the device comprises a first waste collecting chamber which is part of the first member, and a second waste collecting chamber which is part of the second member.

According to some embodiments of the invention the second member is partitioned into a plurality of partitions, each constituted for holding one pipette tip.

According to some embodiments of the invention the partitions are not isolated from each other.

According to some embodiments of the invention the partitions are isolated from each other.

According to some embodiments of the invention a number of the partitions equals at least a number of the assays.

According to some embodiments of the invention the wells comprise at least one well containing a first antibody immobilized on a solid magnetic carrier, and at least one well containing a second antibody labeled with labeling substance, and wherein the antibodies are selected to specifically bind to a target substance in the liquid (*e.g.*, body liquid).

According to some embodiments of the invention the labeling substance is an enzyme, and wherein the antibodies and the enzyme are selected for detecting the target substance by a sandwich ELISA test.

According to some embodiments of the invention the antibodies are selected to specifically bind to a protein selected from the group consisting of TRAIL protein, CRP protein and IP-10 protein.

According to some embodiments of the invention the device comprises the disposable pipette tip within the compartment.

According to some embodiments of the invention the first member comprises a cavity constituted for receiving and fittedly holding a container containing the liquid (*e.g.*, body liquid).

According to some embodiments of the invention the cartridge device has a shape defined by a polygonal cross-section along a horizontal plane. According to some embodiments of the invention the cartridge device has a shape of a cuboid.

According to some embodiments of the invention the cartridge device has a shape defined by a round cross-section along a horizontal plane. According to some embodiments of the invention the cartridge device has a shape of cylinder or a cylindrical sector.

According to some embodiments of the invention the cartridge device has a plurality of connectable modular elements each constituted for performing a different assay. According to some embodiments of the invention each modular element having a respective portion of the first and second members, and constituted for performing a different assay. According to some embodiments of the invention at least one modular element has a respective portion of the first member, and one modular element serves as the second member.

According to an aspect of some embodiments of the present invention there is provided a kit for analyzing a liquid (*e.g.*, body liquid), the kit comprising, in separate packaging, the cartridge device and the container.

According to some embodiments of the invention the container has a volume of from about 5 μl to about 500 μl or from about 50 μl to about 350 μl or from about 100 μl to about 300 μl.

According to some embodiments of the invention the container has a flat base.

According to some embodiments of the invention the container comprises a lid. According to some embodiments of the invention the lid is a foldable lid. According to some embodiments of the invention the lid is pierceable. According to some embodiments of the invention the lid is pierceable and foldable. According to some embodiments of the invention the lid is hingedly connected to the container. According to some embodiments of the invention the lid is pierceable and hingedly connected to the container.

According to some embodiments of the invention the container is transparent to visible light.

According to some embodiments of the invention an inner wall of the container is at least partially coated with an anticoagulant.

According to an aspect of some embodiments of the present invention there is provided a system for analyzing a liquid such as, but not limited to, a body liquid. The system comprises: a cartridge holder, adapted for receiving the cartridge device and having a lever system for automatically hinging the second member responsively to the receiving. The system further comprises an internal analyzer system, having an analysis chamber and being configured for analyzing the liquid (*e.g.*, body liquid) when enclosed in the analysis chamber. The system further comprises a robotic arm system carrying a pipette; and a controller configured for controlling the robotic arm system to establish a relative motion between the cartridge device and the pipette such that the pipette sequentially visits at least the cartridge device, the analysis chamber, and the compartment, and releases a tip of the pipette into the compartment.

According to an aspect of some embodiments of the present invention there is provided a system for analyzing a liquid (*e.g.*, body liquid). The system comprises a first cartridge holder, adapted for receiving a first cartridge member having a plurality of wells for performing assays; and a second cartridge holder, adapted for receiving a second cartridge member having a compartment for holding at least one disposable pipette tip, wherein the first and second cartridge holders are optionally and preferably separated from each other. The system can further comprise an internal analyzer system having an analysis chamber, and being configured for analyzing the liquid (*e.g.*, body liquid) when enclosed in the analysis chamber, and a robotic arm system carrying a pipette. The system can further comprise a controller configured for controlling the robotic arm system to establish a relative motion between the cartridge members and the

pipette such that the pipette visits at least the tip compartment, picks up a tip from the compartment, visits the wells, the analysis chamber, and releases a tip of the pipette back into the compartment.

According to some embodiments of the system has dimensions of Xcm×Ycm×Zcm, wherein each of X, Y and Z is from about 75 to about 125, e.g., about 100. According to some embodiments of the system has dimensions of Xcm×Ycm×Zcm, wherein each of X, Y and Z is from about 35 to about 65, e.g., about 50. According to some embodiments of the system has dimensions of Xcm×Ycm×Zcm, wherein each of X, Y and Z is from about 16 to about 30, e.g., about 23. According to some embodiments of the system has dimensions of Xcm×Ycm×Zcm, wherein each of X and Y is from about 20 to about 26, e.g., about 23, and wherein Z is from about 26 to about 34, e.g., about 30.

According to some embodiments of the invention the cartridge device comprises a pierceable film covering the wells, and the controller is configured for controlling the robotic arm system to pierce the film while visiting the cartridge device.

According to some embodiments of the invention the cartridge device comprises a waste collecting chamber, wherein the controller is configured for controlling the robotic arm system to visit the waste collecting chamber after vising the analysis chamber.

According to some embodiments of the invention the second member is partitioned into a plurality of partitions, and the controller is configured for controlling the robotic arm system to release different pipette tips into different partitions.

According to some embodiments of the invention the first member comprises a cavity constituted for receiving and fittedly holding a container containing the liquid (*e.g.*, body liquid), wherein the controller is configured for controlling the robotic arm system to visit the container.

According to some embodiments of the invention the wells comprise at least one well containing a first antibody immobilized on a solid magnetic carrier, and at least one well containing a second antibody labeled with labeling substance, wherein the antibodies are selected to specifically bind to a target substance in the liquid (*e.g.*, body liquid), wherein the a controller is configured for establishing the relative motion such that the pipette aspirates the liquid (*e.g.*, body liquid), the immobilized first antibody and the labeled second antibody into the tip, and wherein the system comprises a magnetic system constituted for separating the solid magnetic carrier, thereby also the target substance, from other components in the tip.

According to some embodiments of the invention the system comprises a heating system.

According to some embodiments of the invention the heating system comprises a stage configured to automatically engage the cartridge device from below responsively to the receiving of the cartridge device.

According to some embodiments of the invention the heating system is configured to heat the cartridge by conduction.

According to some embodiments of the invention the heating system is configured to heat the cartridge device by radiation or convection but without conduction.

According to some embodiments of the invention the analysis chamber is a dark chamber and the analyzer system is an optical analyzer configured for detecting chemiluminescent signals from the pipette tip when the pipette tip is in the dark chamber.

According to some embodiments of the invention an inner wall of the dark chamber is at least partially coated by a reflective coating.

Unless otherwise defined, all technical and/or scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments of the invention, exemplary methods and/or materials are described below. In case of conflict, the patent specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and are not intended to be necessarily limiting.

Implementation of the method and/or system of embodiments of the invention can involve performing or completing selected tasks manually, automatically, or a combination thereof. Moreover, according to actual instrumentation and equipment of embodiments of the method and/or system of the invention, several selected tasks could be implemented by hardware, by software or by firmware or by a combination thereof using an operating system.

For example, hardware for performing selected tasks according to embodiments of the invention could be implemented as a chip or a circuit. As software, selected tasks according to embodiments of the invention could be implemented as a plurality of software instructions being executed by a computer using any suitable operating system. In an exemplary embodiment of the invention, one or more tasks according to exemplary embodiments of method and/or system as described herein are performed by a data processor, such as a computing platform for executing a plurality of instructions. Optionally, the data processor includes a volatile memory for storing instructions and/or data and/or a non-volatile storage, for example, a magnetic hard-disk and/or removable media, for storing instructions and/or data. Optionally, a network connection is

provided as well. A display and/or a user input device such as a keyboard or mouse are optionally provided as well.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

Some embodiments of the invention are herein described, by way of example only, with reference to the accompanying drawings. With specific reference now to the drawings in detail, it is stressed that the particulars shown are by way of example and for purposes of illustrative discussion of embodiments of the invention. In this regard, the description taken with the drawings makes apparent to those skilled in the art how embodiments of the invention may be practiced.

In the drawings:

FIGs. 1A-I are schematic illustrations of a top view (FIG. 1A) a side view (FIGs. 1B, 1H and 1I) and perspective views (FIGs. 1C and 1D-G) of a cartridge device having a first member and a second member, according to some embodiments of the present invention;

FIGs. 2A-I are schematic illustrations of non-limiting examples for arrangements of partitions within a member of the device shown in FIGs. 1A-D, according to some embodiments of the present invention;

FIGs. 3A-K are schematic illustrations of a container suitable for being loaded into a cavity of the device shown in FIGs. 1A-I, according to some embodiments of the present invention;

FIG. 4 is a schematic illustration of a system for analyzing a liquid (*e.g.*, body liquid), according to some embodiments of the present invention;

FIGs. 5A-D are schematic illustrations showing partial laid-open views of the system shown in FIG. 4, according to some embodiments of the present invention;

FIGs. 5E-G are schematic illustrations showing positions of a stage of heating system before (FIG. 5E), during (FIG. 5F) and after (FIG. 5G) a motion of a cam within the system shown in FIG. 4;

FIGs. 6A-C are schematic illustrations of a robotic arm system according to some embodiments of the present invention;

FIG. 7 is a schematic illustration showing an exploded view of an internal analyzer system, according to some embodiments of the present invention;

FIGs. 8A-C are schematic illustrations of a cross-section along a horizontal plane of the internal analyzer system, according to some embodiments of the present invention;

FIG. 9 is a graph showing an optical signal detected from a pipette tip as the pipette tip moves vertically at a constant horizontal position, as obtained in experiments performed according to some embodiments of the present invention;

FIG. 10 is a graph showing a depended of an intensity decay on a horizontal location of the pipette tip, as obtained during experiments performed according to some embodiments of the present invention;

FIGs. 11A-C are schematic illustrations of an operation procedure of the system shown in FIG. 4, according to some embodiments of the present invention;

FIG. 12 is a schematic illustration of a covering label scored with a plurality of patterns to form frangible piercing locations, according to some embodiments of the present invention;

FIGs. 13A and 13B are schematic illustrations of a cartridge device having a first member and a second member that is slideably connected to the first member, according to some embodiments of the present invention.

FIGs. 14A and 14B are schematic illustrations of a cartridge device in which wells are arranged in rows, wherein in each row the wells and the tips are co-linear with each other, according to some embodiments of the present invention; and

FIGs. 15A and 15B are schematic illustrations of a cartridge device in embodiments of the present invention in which the device has a shape of cylinder.

FIGs. 16A-D are schematic illustrations of a member of a cartridge device that contains compartments for pipette tips and a waste collecting chamber, according to some embodiments of the present invention.

FIGs. 17A-F are schematically illustrations of a container for holding liquid (*e.g.*, body liquid), according to some embodiments of the present invention.

FIGs. 18A-C are schematically illustrations of a cartridge device suitable for receiving the container of FIGs. 17A-F, according to some embodiments of the present invention.

DESCRIPTION OF SPECIFIC EMBODIMENTS OF THE INVENTION

The present invention, in some embodiments thereof, relates to a medical device and, more particularly, but not exclusively, to a cartridge and system for analyzing a sample of liquid (*e.g.*, body liquid), such as, but not limited to, blood.

Before explaining at least one embodiment of the invention in detail, it is to be understood that the invention is not necessarily limited in its application to the details of construction and the arrangement of the components and/or methods set forth in the following description and/or

illustrated in the drawings and/or the Examples. The invention is capable of other embodiments or of being practiced or carried out in various ways.

The technique of the present embodiments can optionally and preferably provide an effective means for analysis of body liquid from a subject. The technique of the present embodiments may be used in a wide variety of circumstances including identification and quantification of analytes that are associated with specific biological processes, physiological conditions, disorders or stages of disorders. As such, the technique of the present embodiments have a broad spectrum of utility in, for example, distinction between bacterial and viral infections, disease diagnosis, drug screening, phylogenetic classification, parental and forensic identification, disease onset and recurrence, individual response to treatment versus population bases, and monitoring of therapy.

The techniques of the present embodiments are particularly useful for measuring proteins for the diagnosis of bacterial infections, viral infections and non-bacterial, non-viral diseases. The techniques of the present embodiments can optionally and preferably employ pattern recognition algorithms for the identification of the type of infection a subject is suffering from, which in turn allows for the selection of an appropriate treatment regimen. Various embodiments of the invention address limitations of current diagnostic solutions by: (i) allowing accurate diagnostics on a broad range of pathogens; (ii) enabling rapid diagnosis (within minutes); (iii) insensitivity to the presence of non-pathogenic bacteria and viruses (thus reducing the problem of false-positive); and (iv) eliminating the need for direct sampling of the pathogen, thus enabling diagnosis of inaccessible infections. Thus, some methods of the invention allow for the selection of subjects for whom antibiotic treatment is desired and prevent unnecessary antibiotic treatment of subjects having only a viral infection or a non-infectious disease. Some methods of the invention also allow for the selection of subjects for whom anti-viral treatment is advantageous.

While some of the embodiments described herein relate to applications directed to the diagnosis of bacterial infections, viral infections and non-bacterial, non-viral diseases distinction, it is to be understood that many other applications can benefit from the technique of the present embodiments, and are therefore encompassed by at least some embodiments of the present disclosure.

FIGs. 1A-I are schematic illustrations of a top view (FIG. 1A) a side view (FIGs. 1B, 1H and 1I) and perspective views (FIGs. 1C and 1D-G) of a cartridge device **10** suitable for analyzing a liquid (*e.g.*, body liquid), according to some embodiments of the present invention. Cartridge device **10** is particularly useful for loading to a system that is configured for automatically performing the analysis, such as, but not limited to, an automatic POC system. A

representative example of a system suitable for receiving cartridge device **10** is provided below. Cartridge device **10** can be used during analysis of any type of body liquid, particularly a mammalian body liquid, *e.g.*, a body liquid of a human.

Representative examples of body liquids contemplated according to some embodiments of the present invention include, without limitation, whole blood, a fraction of whole blood, capillary blood, serum, plasma, urine, saliva, semen, stool, sputum, cerebral spinal fluid, tears, sweat, interstitial fluid, mucus, nasal mucus, amniotic fluid, sample collected by a nasal swab, or the like. In some embodiments of the present invention cartridge device **10** is used during analysis of a whole blood of a human, in some embodiments of the present invention cartridge device **10** is used during analysis of a fraction of whole blood of a human, in some embodiments of the present invention cartridge device **10** is used during analysis of a capillary blood of a human, in some embodiments of the present invention cartridge device **10** is used during analysis of a serum of a human, and in some embodiments of the present invention cartridge device **10** is used during analysis of a plasma of a human. The cartridge device **10** also suitable for analyzing a liquid other than a body fluid, such as, but not limited to, a liquid sample from river, a liquid sample from sewage, a liquid sample from water reservoir, a liquid sample from food product, *etc*.

Cartridge device **10** optionally and preferably comprises a first member **12** having a plurality of wells **14** for performing assays. Wells **14** are shown arranged in a rectangular array, but other arrangements (*e.g.*, circular array, honeycomb array, *etc*.) are also contemplated.

At least a portion of wells **14** contains substances for mixing with the liquid (*e.g.*, body liquid) in order to allow performing the assays. Typically, one or more wells can contain reactive substances (*e.g.*, antibodies) that react with one or more target substances (*e.g.*, antigens) in the body liquid (*e.g.*, by forming immune complexes) once contact is establish between the reactive substance in the respective well and the body liquid. One or more wells can also contain a diluent for diluting the body liquid. One or more wells can also contain a wash buffer for allowing performing assays including a wash step. As a representative example, which is not to be considered as limiting, wells **14a** can contain reactive substances, wells **14b** can contain a diluent, and wells **14c** can contain a wash buffer, but any of wells **14** can potentially include any of the above, or other substances, as desired.

Preferably, cartridge device **10** comprises a pierceable film **22** covering wells **14** to seal wells **14** and to maintain the respective substances within wells **14**, thereby preventing evaporation, flow-out, drop and/or contamination during transportation of device **10** and optionally and preferably also while loading device **10** to a receiving system, such as, but not

limited to, a POC system. Pierceable film **22** can be of any type, such as, but not limited to, an aluminum laminate foil, a plastic film or the like.

The substances in wells **14** are optionally and preferably selected for use in an immunological assay utilizing an antigen-antibody reaction. Representative examples of immunological assays suitable for the present embodiments include, without limitation, an enzyme-linked immunosorbent assay (ELISA), particularly but not necessarily a sandwich ELISA, a chemiluminescent immunoassay, an immunofluorescence assay, a radioimmunoassay, immunochromatography and immunonephelometry.

For example, wells **14** can comprise one or more wells containing a first antibody immobilized on a solid carrier, optionally and preferably a solid magnetic carrier, and one or more wells containing a second antibody labeled with labeling substance, wherein the first and second antibodies are selected to specifically bind to the target substance in the body liquid. The labeling enzyme and the antibodies are optionally and preferably selected for detecting the target substance by a sandwich ELISA.

Labeling substances suitable for use according to some embodiments of the present invention include, without limitation, enzymes, free radicals, radioisotopes, fluorescent dyes, bacteriophages, or coenzymes. Representative examples of suitable enzymes including, without limitation, horseradish peroxidase and alkaline phosphatase. Representative examples of suitable fluorescent labels including, without limitation, fluorescein, Alexa, green fluorescent protein and rhodamine.

The antibodies may be monoclonal, polyclonal, chimeric, or a fragment of the foregoing, and the step of detecting the reaction product may be carried out with any suitable immunoassay.

Suitable sources for antibodies suitable for use according to some embodiments of the present invention include, without limitation, commercially available sources such as, for example, Abazyme, Abnova, AssayPro, Affinity Biologicals, AntibodyShop, Aviva bioscience, Biogenesis, Biotechne, Biosense Laboratories, Calbiochem, Cell Sciences, Chemicon International, Chemokine, Clontech, Cytolab, DAKO, Diagnostic BioSystems, eBioscience, Endocrine Technologies, Enzo Biochem, Eurogentec, Fusion Antibodies, Genesis Biotech, GloboZymes, Haematologic Technologies, Immunodetect, Immunodiagnostik, Immunometrics, Immunostar, Immunovision, Biogenex, Invitrogen, Jackson ImmunoResearch Laboratory, KMI Diagnostics, Koma Biotech, LabFrontier Life Science Institute, Lee Laboratories, Lifescreen, Maine Biotechnology Services, Mediclone, MicroPharm Ltd., ModiQuest, Molecular Innovations, Molecular Probes, Neoclone, Neuromics, New England Biolabs, Novocastra, Novus Biologicals, Oncogene Research Products, Orbigen, Oxford Biotechnology, Panvera,

PerkinElmer Life Sciences, Pharmingen, Phoenix Pharmaceuticals, Pierce Chemical Company, Polymun Scientific, Polysiences, Inc., Promega Corporation, Proteogenix, Protos Immunoresearch, QED Biosciences, Inc., R&D Systems, Repligen, Research Diagnostics, Roboscreen, Santa Cruz Biotechnology, Seikagaku America, Serological Corporation, Serotec, SigmaAldrich, StemCell Technologies, Synaptic Systems GmbH, Technopharm, Terra Nova Biotechnology, TiterMax, Trillium Diagnostics, Upstate Biotechnology, US Biological, Vector Laboratories, Wako Pure Chemical Industries, Zeptometrix, Thermo Fischer scientific, Invitrogen, ATCC, Novus biologicals, Hytest, Medix, and Biospacific. However, the skilled artisan can routinely make antibodies, against any of the proteins described herein.

Polyclonal antibodies for measuring proteins include without limitation antibodies that were produced from sera by active immunization of one or more of the following: Rabbit, Goat, Sheep, Chicken, Duck, Guinea Pig, Mouse, Donkey, Camel, Rat and Horse.

Examples of additional reactive substances, include without limitation: scFv, dsFv, Fab, sVH, $F(ab')_2$, Cyclic peptides, Haptamers, A single-domain antibody, Fab fragments, Single-chain variable fragments, Affibody molecules, Affilins, Nanofitins, Anticalins, Avimers, DARPins, Kunitz domains, Fynomers and Monobody.

In some embodiments of the present invention the target substance in the body liquid is TRAIL. Antibodies suitable for measuring TRAIL include without limitation: Mouse, Monoclonal (55B709-3) IgG (Thermo Fisher Scientific); Mouse, Monoclonal (2E5) IgG1 (Enzo Lifesciences); Mouse, Monoclonal (2E05) IgG1; Mouse, Monoclonal (M912292) IgG1 kappa (My BioSource); Mouse, Monoclonal (IIIF6) IgG2b; Mouse, Monoclonal (2E1-1B9) IgG1 (EpiGentek); Mouse, Monoclonal (RIK-2) IgG1, kappa (BioLegend); Mouse, Monoclonal M181 IgG1 (Immunex Corporation); Mouse, Monoclonal VI10E IgG2b (Novus Biologicals); Mouse, Monoclonal MAB375 IgG1 (R&D Systems); Mouse, Monoclonal MAB687 IgG1 (R&D Systems); Mouse, Monoclonal HS501 IgG1 (Enzo Lifesciences); Mouse, Monoclonal clone 75411.11 Mouse IgG1 (Abcam); Mouse, Monoclonal T8175-50 IgG (X-Zell Biotech Co); Mouse, Monoclonal 2B2.108 IgG1; Mouse, Monoclonal B-T24 IgG1 (Cell Sciences); Mouse, Monoclonal 55B709.3 IgG1 (Thermo Fisher Scientific); Mouse, Monoclonal D3 IgG1 (Thermo Fisher Scientific); Goat, Polyclonal C19 IgG; Rabbit, Polyclonal H257 IgG (Santa Cruz Biotechnology); Mouse, Monoclonal 500-M49 IgG; Mouse, Monoclonal 05-607 IgG; Mouse, Monoclonal B-T24 IgG1 (Thermo Fisher Scientific); Rat, Monoclonal (N2B2), IgG2a, kappa (Thermo Fisher Scientific); Mouse, Monoclonal (1A7-2B7), IgG1 (Genxbio); Mouse, Monoclonal (55B709.3), IgG (Thermo Fisher Scientific); Mouse, Monoclonal B-S23* IgG1 (Cell Sciences), Human TRAIL/TNFSF10 MAb (Clone 75411), Mouse IgG1 (R&D Systems); Human

TRAIL/TNFSF10 MAb (Clone 124723), Mouse IgG1 (R&D Systems) and Human TRAIL/TNFSF10 MAb (Clone 75402), Mouse IgG1 (R&D Systems).

Antibodies for measuring TRAIL include monoclonal antibodies and polyclonal antibodies for measuring TRAIL. Antibodies for measuring TRAIL include antibodies that were developed to target epitopes from the list comprising of: Mouse myeloma cell line NS0-derived recombinant human TRAIL (Thr95-Gly281 Accession # P50591), Mouse myeloma cell line, NS0-derived recombinant human TRAIL (Thr95-Gly281, with an N-terminal Met and 6-His tag Accession # P50591), E. coli-derived, (Val114-Gly281, with and without an N-terminal Met Accession #:Q6IBA9), Human plasma derived TRAIL, Human serum derived TRAIL, recombinant human TRAIL where first amino acid is between position 85 – 151 and the last amino acid is at position 249 - 281.

In some embodiments of the present invention the target substance in the body liquid is CRP. Examples of monoclonal antibodies suitable for measuring CRP include without limitation: Mouse, Monoclonal (108-2A2); Mouse, Monoclonal (108-7G41D2); Mouse, Monoclonal (12D-2C-36), IgG1; Mouse, Monoclonal (1G1), IgG1; Mouse, Monoclonal (5A9), IgG2a kappa; Mouse, Monoclonal (63F4), IgG1; Mouse, Monoclonal (67A1), IgG1; Mouse, Monoclonal (8B-5E), IgG1; Mouse, Monoclonal (B893M), IgG2b, lambda; Mouse, Monoclonal (C1), IgG2b; Mouse, Monoclonal (C11F2), IgG; Mouse, Monoclonal (C2), IgG1; Mouse, Monoclonal (C3), IgG1; Mouse, Monoclonal (C4), IgG1; Mouse, Monoclonal (C5), IgG2a; Mouse, Monoclonal (C6), IgG2a; Mouse, Monoclonal (C7), IgG1; Mouse, Monoclonal (CRP103), IgG2b; Mouse, Monoclonal (CRP11), IgG1; Mouse, Monoclonal (CRP135), IgG1; Mouse, Monoclonal (CRP169), IgG2a; Mouse, Monoclonal (CRP30), IgG1; Mouse, Monoclonal (CRP36), IgG2a; Rabbit, Monoclonal (EPR283Y), IgG; Mouse, Monoclonal (KT39), IgG2b; Mouse, Monoclonal (N-a), IgG1; Mouse, Monoclonal (N1G1), IgG1; Monoclonal (P5A9AT); Mouse, Monoclonal (S5G1), IgG1; Mouse, Monoclonal (SB78c), IgG1; Mouse, Monoclonal (SB78d), IgG1 and Rabbit, Monoclonal (Y284), IgG, Human C-Reactive Protein/CRP Biot MAb (Cl 232024), Mouse IgG2B, Human C-Reactive Protein/CRP MAb (Clone 232007), Mouse IgG2B, Human/Mouse/Porcine C-Reactive Protein/CRP MAb (Cl 232026), Mouse IgG2A, Mouse, C-reactive protein (CRP) monoclonal antibody (clone A58014501); Mouse, C-reactive protein (CRP) monoclonal antibody (clone A58015501).

Antibodies for measuring CRP include monoclonal antibodies for measuring CRP and polyclonal antibodies for measuring CRP.

Antibodies for measuring CRP also include antibodies that were developed to target epitopes from the list comprising of: Human plasma derived CRP, Human serum derived CRP,

Mouse myeloma cell line NS0-derived recombinant human C-Reactive Protein/CRP (Phe17-Pro224 Accession # P02741).

In some embodiments of the present invention the target substance in the body liquid is IP-10. Examples of monoclonal antibodies suitable for measuring IP-10 include without limitation: IP-10 / CXCL10 Mouse anti-Human Monoclonal (4D5) Antibody (LifeSpan BioSciences), IP-10 / CXCL10 Mouse anti-Human Monoclonal (A00163.01) Antibody (LifeSpan BioSciences), MOUSE ANTI HUMAN IP-10 (AbD Serotec) , RABBIT ANTI HUMAN IP-10 (AbD Serotec), IP-10 Human mAb 6D4 (Hycult Biotech), Mouse Anti-Human IP-10 Monoclonal Antibody Clone B-C50 (Diaclone), Mouse Anti-Human IP-10 Monoclonal Antibody Clone B-C55 (Diaclone), Human CXCL10/IP-10 MAb Clone 33036 (R&D Systems), Human CXCL10/IP-10/CRG-2 MAb Clone 33021 (R&D Systems), Human CXCL10/IP-10/CRG-2 MAb Clone 33033 (R&D Systems), CXCL10/INP10 Antibody 1E9 (Novus Biologicals), CXCL10/INP10 Antibody 2C1 (Novus Biologicals), CXCL10/INP10 Antibody 6D4 (Novus Biologicals), CXCL10 monoclonal antibody M01A clone 2C1 (Abnova Corporation), CXCL10 monoclonal antibody (M05), clone 1E9 (Abnova Corporation), CXCL10 monoclonal antibody, clone 1 (Abnova Corporation), IP10 antibody 6D4 (Abcam), IP10 antibody EPR7849 (Abcam), IP10 antibody EPR7850 (Abcam).

Antibodies for measuring IP-10 include monoclonal antibodies for measuring IP-10 and polyclonal antibodies for measuring IP-10.

Antibodies for measuring IP-10 also include antibodies that were developed to target epitopes from the list comprising of: Recombinant human CXCL10/IP-10, non-glycosylated proteins chain containing 77 amino acids (aa 22-98) and an N-terminal His tag Interferon gamma inducible protein 10 (125 aa long), IP-10 His Tag Human Recombinant IP-10 produced in *E.Coli* containing 77 amino acids fragment (22-98) and having a total molecular mass of 8.5 kDa with an amino-terminal hexahistidine tag, E. coli-derived Human IP-10 (Val22-Pro98) with an N-terminal Met, Human plasma derived IP-10, Human serum derived IP-10, recombinant human IP-10 where first amino acid is between position 1-24 and the last amino acid is at position 71-98.

Further exemplary target substances in the body liquid that can be measured in some embodiments of the present invention to assist in distinguishing between bacterial and viral infections include: IL1RA, Mac-2BP, B2M, BCA-1, CHI3L1, Eotaxin, IL1a, MCP, CD62L, VEGFR2, CHP, CMPK2, CORO1C, EIF2AK2, ISG15, RPL22L1, RTN3, CD112, CD134, CD182, CD231, CD235A, CD335, CD337, CD45, CD49D, CD66A/C/D/E, CD73, CD84, EGFR, GPR162, HLA-A/B/C, ITGAM, NRG1, RAP1B, SELI, SPINT2, SSEA1, IgG non-

specific bound molecules, IL1, I-TAC, TNFR1, L11, CD8A, , IL7, SAA, TREM-1, PCT, IL-8, IL-6, ARG1, BCA-1, BRI3BP, CCL19/ MIP3b, MCP-2, ABTB1, ADIPOR1, ARHGDIB, ARPC2, ATP6V0B, C1orf83, CD15, CES1, CORO1A, CRP, CSDA, EIF4B, EPSTI1, GAS7, HERC5, IFI6, KIAA0082, IFIT1, IFIT3, IFITM1, IFITM2, IFITM3, LIPT1, IL7R, ISG20, LOC26010, LY6E, LRDD, LTA4H, MAN1C1, MBOAT2, MX1, NPM1, OAS2, PARP12, PARP9, QARS, RAB13, RAB31, RAC2, RPL34, PDIA6, PTEN, RSAD2, SART3, SDCBP, SMAD9, SOCS3, TRIM 22, UBE2N, XAF1 and ZBP1.

In some embodiments of the present invention the target substance in the body liquid is originated from or secreted by micro-organisms including bacteria, viruses, parasites (for example Toxoplasma gondii) or fungi. These target proteins could be any type of bacterial, viral or fungal protein including for example structural proteins, functional proteins and enzymes (for example hemagglutinin and neuraminidase of the influenza virus), secreted proteins, and microbial toxins (for example botulinum toxin produced by the bacterium *Clostridium botulinum*). Examples of viruses include but not limited to: Influenza A virus (Flu A), Influenza B virus (Flu B), Respiratory syncytial virus A (RSV A), Respiratory syncytial virus B (RSV B), Flu A-H1, Flu A-H1pdm09, Flu A-H3, Adenovirus (AdV), Enterovirus (HEV), Parainfluenza virus 1 (PIV 1), Parainfluenza virus 2 (PIV 2), Parainfluenza virus 3 (PIV 3), Parainfluenza virus 4 (PIV 4), Metapneumovirus (MPV), Bocavirus (HBoV), Rhinovirus (HRV), Coronavirus NL63 (CoV NL63), Coronavirus 229E (CoV 229E), Coronavirus OC43 (CoV OC43), Rotavirus, Smallpox, Ebola virus, Hepatitis A virus, Hepatitis C, Hepatitis B, Rubella virus, Varicella-Zoster Virus, Epstein-Barr virus, Herpes Simplex Virus, Cytomegalovirus, Measles and Mumps.

Examples of bacteria include but not limited to: Mycoplasma pneumoniae (MP), Chlamydophila pneumoniae (CP), Legionella pneumophila (LP), Haemophilus influenzae (HI), Streptococcus pneumoniae (SP), Bordetella pertussis (BP), Bordetella parapertussis (BPP), Group A streptococcus, Group B streptococcus, E coli, bacillus anthracis, francisella tularensis, Burkholderia pseudomallei, Treponema pallidum, Borrelia burgdorferi and Helicobacter pylori.

In some embodiments of the present invention the measurement of micro-organism target substance is used to detect the presence of a specific pathogenic or non-pathogenic micro-organism in the body liquid. In some embodiments of the present invention measurement of micro-organism target substance is used to quantify the levels of a specific pathogenic or non-pathogenic micro-organism in the body liquid in order to evaluate the viral or bacterial load.

The techniques of the present embodiments can also be used to measure other types of physiological markers that may help to diagnose or monitor various disease states, response to treatment, injury and biothreat exposure including for example inflammatory markers, cardiac

markers, metabolic markers, endocrine markers, neurodegenerative markers, neuronal marker and cancer markers. Examples of physiological markers include: Troponin, Troponin I, TroponinT, Highly sensitive troponin, BNP, IGF-1, CK-MB, Myoglobin, CPK, AP, PTH, Galectin-3, Galectin-1, highly sensitive CRP, Ubiquitin C- terminal Hydrolase-L1 (UCH-L1), Glial Fibrillary Acidic Protein (GFAP), CKB, Hemoglobin A and Hemoglobin B.

In some embodiments of the present invention one or more of the wells contains an inhibitory solution, such as, but not limited to, a metal chelating agent, e.g., EDTA or EGTA, or an enzyme inhibitor, e.g., thepohylline, vanadate or arsenate.

According to some embodiments of the present invention at least one of the wells has a tapered (*e.g.*, conical) base. A well with a tapered base shaped has an advantage of ensuring high surface tension of the enclosed liquids, thereby preventing liquid from accumulating at the top part of the well, for example, during transportation. It was found by the inventors that it is particularly advantageous when one or more of the wells that contain the reagents (*e.g.*, antibodies) are tapered, since the cartridge device is typically transported while the reagents are already contained within the wells.

According to some embodiments of the present invention at least one of the wells has a non-tapered base. Such a shape has an advantage that, compared to the tapered well, it has a lower risk of bubble formation when liquid is introduced into the well, for example, by pipetting during an assay. It was found by the inventors that this is particularly advantageous when the wells that are designated to contain the liquid are non-tapered, since the assay is typically performed by adding a sample of the liquid (*e.g.*, body liquid) to the well.

Thus, the present embodiments contemplate a cartridge device that comprises a first plurality of wells, each having a tapered base; and a second plurality of wells. The two pluralities of wells are formed in a monolithic structure. At least some of the wells of the first plurality of wells contain a reagent therein. In some embodiments of the present invention one or more of the wells of the first plurality of wells is empty. One or more of the wells of the second plurality of wells is empty. In use, one or more of the empty wells of the second plurality of wells is optionally and preferably filed with a liquid to be analyzed, such as, but not limited to, a body liquid. Optionally, one or more of the wells of the second plurality of wells contain a reagent therein.

Referring again to FIGs. 1A-I, cartridge device **10** optionally and preferably comprises a waste collecting chamber **24** (see, FIG. 1D). Waste collecting chamber **24** can optionally and preferably, but not necessarily, comprise a moisture absorber (not shown), such as, but not limited to, a hygroscopic material, a sponge, cellulose fibers, a charcoal, an activated charcoal, a

molecular sieve, and/or one or more moisture absorbing substances including, without limitation, a salt, lithium chloride, calcium chloride, magnesium chloride, phosphorus pentaoxide, silica gel, zeolite, sodium sulfate, activated alumina and activated carbon. Use of hygroscopic material is particularly advantageous since it assists in reducing probability of biohazard. A contaminated fluid is less likely to escape from the waste chamber because it is entrapped within the hygroscopic material. In some embodiments of the present invention waste collecting chamber **24** extends to beneath, but is physically separated from, wells **14**.

The waste collecting chamber is optionally and preferably covered by a structure (not shown) such as, but not limited to, a pierceable foil, a non-flexible openable lid, a flexible openable lid, and a one way valve. For example, the structure covering the waste collecting chamber can be a foil, which is pierced to expose a waste collecting chamber before deposing waste to it. The sealing foil is optionally capable of being pierced several times in the same location.

The covering structure can optionally and preferably be in a form of a labyrinth, so that the waste can only escape the cartridge if the device is rotated and inverted in a very specific manner. This significantly reduces the probability for the liquid to inadvertently escape the cartridge. Such a covering structure can be used to cover only the waste collecting chamber **24**, or only the wells **24**, or both the waste collecting chamber **24** and the wells **14**.

While FIG. 1D illustrates waste collecting chamber **24** as a having single chamber, this need not necessarily be the case, since, the present embodiments also contemplate waste collecting chamber haven multiple separated chambers or sub-chamber, that may be connected thereamongst of separated from each other, for example, by sponge or hygroscopic partition that absorbs waste. These embodiments are particularly useful when it is desired not to access the same preventing the same waste collecting chamber more than once, in which caser each chamber is a single use chamber, into which there is a single deposing of waste. Alternatively, or additionally, the waste collecting chamber can comprise several entrance points.

The waste collecting chamber sealing foil or the wells sealing foil can be covered by a label **200**, as illustrated in FIG. 12. Optionally and preferably the covering label **200** is scored or partially cut along a pattern **202** to form a frangible piercing location defined by pattern **202**. Optionally and preferably there is a plurality of frangible piercing locations, each defined by a respective scored pattern, as illustrated in FIG. 12. Two or more adjacent scored patterns (e.g., each pair of adjacent scored patterns) can be separated from each other. The scored pattern has a shape of, for example, a cross or a star. The cross can be a right angle cross, e.g., shape of a plus symbol, or an acute angle cross, e.g., shape of an X symbol. In some embodiments of the present

invention two or more adjacent scored patterns (e.g., each pair of adjacent scored patterns) have shapes of differently oriented crosses or differently shaped crosses, to ensure that the scored patterns are separated from each other. Separating between the scored patterns is advantage from the standpoint of preventing cross-talk between different entry locations to the chamber or different wells.

According to some embodiments of the invention, the scored patterns comprise right angle crosses, e.g., shape of plus symbols, and acute angle crosses, e.g., shape of X symbols, arranged in alternating manner.

Cartridge device **10** optionally and preferably comprises a second member **16**. In some embodiments of the present invention second member **16**, is connected to first member **12**. In preferred embodiments of the invention second member **16** is connected to first member **12** by a hinge **18** (FIG. 1D) allowing a rotation of one of the two members **12** and **16** with respect to the other about hinge **18**. Preferably, hinge **18** is configured to allow rotation to form an angle of at least 70° or at least 80° or at least 90° between members **12** and **16**.

The second member **16** can in some embodiments of the present invention be slideably connected to first member **12**, as schematically illustrated in FIGs. 13A and 13B. In these embodiments, device **10** can be distributed to the users in a state in which second member **16** covers or partially covers first member **12**. In use, second member **16** can slide over first member **12** to expose the wells (or the structure, such as, but not limited to, the sealing foil or label that covers the wells, when employed). Following this sliding, the second member **16** can be completely detached from first member **12**, or can remain hinged to first member **12** in a similar manner that is illustrated in FIGs. 1D-F. In embodiments in which second member **16** slides over first member **12**, the length of device **10** is shorter than in embodiments in which the members **12** and **16** are connected by hinge **18**.

The second cartridge member can in some embodiments of the present invention be separated from the first cartridge member in a manner that they are not to be connected. These embodiments are useful when it is desired to load the two cartridge members separately to a system that is configured for automatically performing the analysis, such as, but not limited to, an automatic POC system.

Second member **16** optionally and preferably comprises a compartment **20** (shown in FIGs. 1D and 1E) for holding at least one disposable pipette tip **111** (shown in FIGs. 1A, 1B and 1D). Optionally, as illustrated in FIG. 1D, when first member **12** is held horizontally, and second member **16** is rotated downwards about hinge **18**, the compartment **20** holds the pipette tips in a generally upright orientation (*e.g.*, with a deviation of ±20° relative to the direction of gravity).

In various exemplary embodiments of the one or more disposable pipette tips **111** are already within compartment **20**, preferably in sterile condition, before the aforementioned rotation of one of the members **12** and **16** (see FIGs. 1A and 1B)

In some embodiments of the present invention waste collecting chamber **24** is covered by a lid **26** connected to or being an extension of second member **16**. In these embodiments, when second member **16** is hinged to a generally upright orientation, lid **26** is hinged together with second member **16** and collecting chamber **24** is exposed, as illustrated in FIG. 1D.

The present embodiments also contemplate configurations in which the waste collecting chamber **24** is part of the second member **16**. Representative examples of these embodiments are illustrated in FIGs. 16A-D. Also contemplated, are embodiments in which there is a first waste collecting chamber **24** which is part of first member **12**, and a second waste collecting chamber which is part of the second member **16**.

Cartridge device **10** can optionally and preferably comprise one or more identifiers **34** disposed on one of its external walls. In the illustrations of FIGs. 1A and 1C, which are not to be considered as limiting, identifier **34** is on the upper wall of member **16**, but any other wall can be used to carry identifier **34**. Further, more than one identifier can be used, on a respective more than one wall. Identifier **34** can be embossed, debossed or printed, and can be of any type such as, but not limited to, a set of machine-readable symbols, *e.g.*, one-dimensional or barcode symbols, two-dimensional or matrix or area code symbols, or combinations thereof. Also contemplated are other types of identifiers, including, without limitation, a magnetic recording device, an electronic chip, such as, but not limited to, an RFID chip, or the like.

Identifier **34** can optionally and preferably encode information pertaining to the contents of wells **14** and/or to the identity of the subject whose body liquid is to be analyzed. Identifier **34** can, in some embodiments of the present invention, encode other types of information, such as, but not limited to, information on the type of target substance to be analyzed, reagent management information, and information on a calibration curve for use in the analysis. When an automatic system, *e.g.*, a POC system, is provided with a device that reads the information from identifier **34**, the operator of the system can merely load cartridge device **10** to such a system without the need to manually operate a work sheet, which is a major cause of an error in conventional POC settings. In some embodiments of the present invention the record of the information on identifier **34** is configured to be destroyed once cartridge device **10** is used, so as to allow determining whether a particular cartridge device item has been used or is unused. This, can be done, for example, by providing identifier **34** on a seal of film, such as, but not limited to, film **22**, that needs to be pierced or broken before performing the assay.

In some embodiments of the present invention compartment **20** of second member **16** is partitioned into a plurality of partitions **28**, each constituted for holding one pipette tip. The partitions can be isolated from each other (namely devoid of fluid communication thereamongst). Alternatively, partitions can be partial in which case partitions **28** are not isolated from each other, and allow some fluid communication thereamongst.

Partitions **28** can be arranged in any geometrical arrangement within compartment **20**. Non-limiting examples for arrangements of partitions **28** in member **16** are illustrated in FIGs. 2A-I. FIGs. 2A, 2D and 2G illustrate the internal arrangement of partitions **28** in compartment **20**, FIGs. 2B, 2E and 2H respectively show cartridge device when member **16** is not hinged, and FIGs. 2C, 2F and 2I respectively show a perspective view of member **16** once hinged to a vertical orientation. In FIGs. 2A-C, the cross sections of partitions **28** are arranged along the sides of a trapezoid, in FIGs. 2D-F, the cross sections of partitions **28** are arranged along the sides of a square, and in FIGs. 2G-I, the cross sections of partitions **28** are arranged along a straight. Arrangements to form other geometrical shapes are also contemplated. Although FIGs. 2A-I all show four partitions in compartment **20**, this need not necessarily be the case, since, for some applications, more or less than four partitions can be employed. Preferably, the number of partitions equals at least the number of assays for which device **10** is to be used.

Aside for holding the substances in wells **14** and the disposable tips **111** in compartment **20**, device **10** is preferably also configured for holding the liquid (*e.g.*, body liquid). This can be done in more than one way.

In some embodiments of the present invention device **10** comprises a sample chamber **30** for holding the liquid (e.g., body liquid). Chamber **30** can be enacted by one of well **14** or it can be an additional chamber of device **10**, as desired. In embodiments in which cartridge device **10** comprises pierceable film **22**, film **22** preferably covers all wells **14** except chamber **30**, as illustrated in FIGs. 2B, 2E and 2H.

In some embodiments of the present invention the liquid (*e.g.*, body liquid) is provided in a separate container. In these embodiments, first member **12** of device **10** optionally and preferably comprises a cavity **32** constituted for receiving and fittedly holding a container **40** (not shown in FIGs. 1A-D, see FIGs. 3A-K) containing the liquid (e.g., body liquid).

Any of the above configurations for introducing the liquid (*e.g.*, body liquid) into device **10** can be used for any type of liquid (*e.g.*, body liquid). A preferred, albeit not exclusive, use of container **40** is when the body liquid is a whole blood or capillary blood sample, and a preferred, albeit not exclusive, use of chamber **30** is for other types of body liquids, *e.g.*, a serum, a nasal mucus sample, *etc*. The procedure for loading the body liquid into device **10** may optionally, but

not necessarily, also be selected based on the clinical setting in which the operation. For example, use of container **40** is advantageous at a POC clinic, and use of chamber **30** is advantageous at facilities with a central laboratory (*e.g.*, hospitals or research facilities).

Cartridge device **10** can, in some embodiments of the present invention, include both chamber **30** and cavity **32**. In these embodiments, when cartridge device **10** is intended for analysis of a liquid (e.g. body liquid) contained in chamber **30** (*e.g.*, for analysis of serum collected in a hospital), cavity **32** is optionally sealed and is not in use, and when cartridge device **10** is intended for analysis of a liquid (*e.g.*, body liquid) contained in container **40** (*e.g.*, analysis of capillary blood collected at a POC facility), chamber **30** is optionally sealed and is not in use. In some embodiments of the present invention cartridge device **10** is accompanied by instructions for use. For example, when cavity **32** is sealed the instructions can include an indication that the liquid (*e.g.*, body liquid) is to be introduced into chamber **30** and that cavity **32** is not to be used, and when chamber **30** is sealed the instructions can include an indication that the liquid (*e.g.*, body liquid) is to be introduced into a separate container (*e.g.*, container **40** described below) which is to be loaded into cavity **32** of device **10**, and that chamber **30** is not to be used.

Also contemplated, are embodiments in which the operator is allowed to use both container **40** and chamber **30**. In these embodiments, container **40** and chamber **30** optionally and preferably contain different types of liquids (*e.g.*, different types body liquids). Any combination of different types of liquids, such as, but not limited to, the types of body liquids listed above, is contemplated. Loading two different types of body liquids into the same cartridge device is useful, when it is desired to detect the presence or measure the level of more than one target substance, wherein at least two target substances potentially reside in different types of body liquids. For example, one type of body liquid can be used for detecting the presence or measuring the level of a target substance indicative of the subject's response to a potential infection, and another type of body liquid can be used for detecting the presence or measuring the level of a target substance indicative of presence or level of a disease causing agent, such as, but not limited to, a micro-organism (*e.g.*, a bacterium, a virus or a fungus). As a representative example, which is not to be considered as limiting, container **40** can contain a capillary blood sample, and chamber **30** can contain a nasal mucus sample. The capillary blood sample in container **40** can be analyzed to detect, *e.g.*, host proteins, and the nasal mucus sample can be analyzed to detect, *e.g.*, micro-organism related proteins.

The present embodiments also contemplate configurations in which the two members **12** and **16** are co-linear with each other. Such a configuration is illustrated in FIGs. 14A and 14B. Shown is a configuration in which wells are arranged in rows, wherein in each row the wells **14**

and the partition **28** are co-linear with each other. Each row provides the substances and tip that are to be used in a single assay. Specifically, the wells **14** at a particular row contain the substances that are to be used for the assay, and the partition **28** at that particular row contains the tip **111** in which the assay is to be executed as described below. The cavity **32** for receiving container **40** and the waste collecting chamber **24** can be arranged on a separate row.

Device **10** can have several connectable modular elements, each optionally having a respective portion of the first and second members, and constituted for performing a different assay. For example, when the wells **14** and the partition **28** are co-linear with each other and are arranged in rows, the rows can enact the modular elements. This embodiment is illustrated in FIG. 14B showing a modular element **11a** in the form of a single row having member **12** with a plurality of wells **14**, and member **16** with a compartment **20** for holding a tip. Several such modular elements **11a** can be assembled together and the tips **111** can be introduced into the compartment **20** of each modular element **11a**. The modular elements **11a** can be further assembled with an additional modular element **11b** that includes cavity **32** for receiving container **40** and the waste collecting chamber **24**, to form the cartridge device illustrated at the right panel of FIG. 14B. The modular approach is advantageous since it allows flexibility with manufacturing line and product pipeline. For example: one modular element **11a** can be fabricated to detect one set of protein (*e.g.*, CRP, IP10 and TRAIL), and another modular element **11a** can be fabricated to detect another set of proteins (*e.g.*, CRP, PCT, ILFLUENZA-related protein and MX1).

Device **10** can have any shape. Preferably, the shape is compatible with a cartridge holder of a system that receives device **10** and performs the analysis (see FIGs. 11A-C). FIGs. 1A through 2I, and 14A and 14B illustrate embodiments in which device **10** has a shape defined by a generally polygonal cross-section along the horizontal plane. For example, device **10** can have a shape of a cuboid, preferably with round edges, or several cuboids preferably with round edges, (e.g., each of members **12** and **16** is shaped as a cuboid with round edges). However, this need not necessarily be the case, since some embodiments of the present invention contemplate a cartridge device with a shape defined by a round cross-section along the horizontal plane. These embodiments are illustrated in FIGs. 15A and 15B. In the embodiment illustrated in FIG. 15A device **10** has a shape of cylinder, but embodiments in which device **10** has shape of a cylindrical sector or other round shapes are also contemplated.

In embodiments in which device **10** has a shape defined by a round cross-section along the horizontal plane (*e.g.*, as illustrated in FIG. 15A), it can also be assembled from a plurality of modular elements. For example, each modular elements can have a shape of a cylindrical sector,

as illustrated in FIG. 15B. In the embodiment illustrated in FIG. 15A, member **12** is assembled from several modular elements **11a**, each containing a plurality of wells **14** and compartment **20** for holding the tips (not shown), but other arrangements are also contemplated according to some embodiments of the present invention.

FIGs. 3A-K are schematic illustrations of a container **40** suitable for being loaded into cavity **32** of device **10**, according to some embodiments of the present invention.

In some embodiments of the present invention container **40** has a flat base **46**. The advantage of these embodiments is that the flat base **46** ensures that container **40** can be stably place on a surface, such as a desk. Another advantage is that the flat base provides more area to attach labels and stickers, such as, but not limited to, identification label. Container **40** optionally and preferably has an internal compartment **42** for holding the liquid (*e.g.*, body liquid). Compartment **42** is typically from about 5 μl to about 500 μl or from about 50 μl to about 350 μl or from about 100 μl to about 300 μl in volume. Such a volume is sufficiently small to be considered non-threatening psychologically, particularly when the subject is a child, but still succulently large to allow accurate measurement of multiple target substances. An inner wall of compartment **42** is optionally and preferably coated, at least partially, with an anticoagulant.

Preferably, compartment **42** is transparent to visible light to provide the practitioner with a view of the liquid (*e.g.*, body liquid). Height reference marks **44** can optionally and preferably be provided on the wall of compartment **42** to indicate the recommended maximum and minimum filling heights of the liquid (*e.g.*, body liquid) within compartment **42**.

Container **40** preferably comprises a lid **48** that seals the internal compartment **42** to preventing coagulation, evaporation, flow-out, drop and/or contamination during transportation of container **40** and optionally and preferably also while loading of container **40** into cavity **32** of device **10**. The lid **48** optionally and preferably prevent the anticoagulant from being exposed to oxygen, hence to preserves its efficacy in preventing coagulation. The lid **48** is also useful since it allows carrying container **40** into from one place to another with reduced or no biohazard exposure. The lid **48** is also useful for allowing to collect several samples in a remote location (e.g, pediatric ward, retirement home).

Lid **48** can be foldable or hingedly connected to the body of container **40**. In some embodiments of the present invention lid **48** is pierceable, to allow extracting samples of the liquid (*e.g.*, body liquid) from compartment **42** for analysis. This can be achieved, for example, by making the portion of lid **48** that is above compartment **42** in the form of a pierceable film **50**. Film **50** the can be of any type, such as, but not limited to, an aluminum laminate foil, a plastic film or the like.

In some embodiments of the present invention container **40** is provided with gripping ribs **52** allowing the operator to hold the container **40** in a comfortable manner.

FIGs. 17A-F are schematically illustrations of container **40** in other embodiments of the present invention. In these embodiments, liquid (blood in the present illustration) is drawn out of the body by a capillary collector **170** having a sealing element **172** (*e.g.*, a sealing rubber) thereon (FIG. 17A). Container **40** can have two cavities: a first cavity **180** receives the capillary collector **170**, and a second cavity **182** is in fluid communication with the first cavity **180** and is constituted to receive from the first cavity **180** liquid **186** drawn out of the capillary collector **170**.

Once the liquid is in capillary collector **170**, capillary collector is introduced (FIG. 17B) into an opening **174** of container **40**, such that sealing element **172** engages the container's body and seals opening **174** (FIG. 17C). Container **40** optionally and preferably has another opening **176** that is covered by a sealing foil **178**. In use, tip **111** is pulled from member **16** of device **10** (FIG. 17E), and is brought into contact with element **172** to pierce element **172** (FIG. 17D). Air or diluent is forced out of tip **111** so as to extract the liquid (*e.g.*, body liquid) out of capillary collector **170**, and into the cavity of container **40** (FIG. 17D). Thereafter, tip **111** is brought into contact with foil **178** to pierce foil **178** and to aspirate the body fluid from container **40** (FIG. 17F). A representative example of a configuration of device **10** suitable for this embodiments is illustrated in FIGs. 18A-C. In these embodiments cavity **32** for receiving container **40** is formed in second member **16**, and container **40** is introduced into cavity in horizontal orientation. Once member **16** is hinged, container **40** assumes a generally upright orientation and the procedure described in FIGs. 17D-F is executed.

Device **10** and container **40** can be provided as a kit for analyzing the liquid (*e.g.*, body liquid). The kit can include device **10** and container **40** in the same packaging or more preferably in separate packaging.

In use of the kit, the lid **48** of container **40** is opened and the liquid (*e.g.*, body liquid) is transferred, preferably directly from the subject, into compartment **42**. For example, when the body liquid is blood, a blood vessel in a finger of the subject can be pierced and the finger of subject can be guided to cover compartment **42** such that the blood exits the blood vessel and enters compartment **42**. The lid **48** is then closed to seal compartment **42**, and container **40** is placed in cavity **32** of device **10**. Preferably, an acoustical indication (*e.g.*, a click) or mechanical detent is effected when container **40** is fittedly placed in its position, for example, by means of a snap-in mechanism (not shown) mounted on container **40** and/or in cavity **32**. Thus, container **40** collects the liquid directly from the subject, and is then placed as is in cartridge device **10**. This is advantageous over conventional blood collecting devices which require a two-step operation in

which first the blood is collected, *e.g.*, by a capillary device, and then transferred from the capillary device to a container.

The advantage of having container **40** as a separate element from cartridge device **10**, is that it allows using of the same cartridge for different sample types, thereby eliminating manufacturing issues. For example, the same type of cartridge device **10** can be used with serum, blood, saliva, and the like. Another advantage is that the cartridge without the liquid sample can be stored in a refrigerator, allowing using container **40** for sampling the liquid away from the cartridge.

Cartridge device **10** and/or container **40** can be made of any material known in the art of disposable devices. In some embodiments, at least one of the components of cartridge device **10** and/or container **40** is constructed of a polymeric material. Non-limiting examples of materials suitable for the present embodiments include polystyrene, polycarbonate, polypropylene, polydimethysiloxanes (PDMS), polyurethane, polyvinylchloride (PVC), polysulfone, polymethylmethacrylate (PMMA), acrylonitrile-butadiene-styrene (ABS), and glass.

Cartridge device **10** and/or container **40** or one or more of the subcomponents thereof can be manufactured by variety of methods including, without limitation, stamping, injection molding, embossing, casting, blow molding, machining, welding, ultrasonic welding, thermal bonding and three-dimensional printing. The subcomponents of cartridge device **10** and/or container **40** can be affixed to each other by any known technique, including, without limitation, thermal bonding, ultrasonic welding, friction fitting (press fitting), adhesives or, a natural adhesion between the two components

FIGs. 4-7 are schematic illustrations of a system **100** for analyzing a liquid (*e.g.*, body liquid), according to some embodiments of the present invention. System **100** can be used as a POC system. System **100** comprises a cartridge holder **102**, adapted for receiving a cartridge device, such as, but not limited to, cartridge device **10**, and an internal analyzer system **104**, having an analysis chamber **106** and being configured for analyzing the liquid (*e.g.*, body liquid) when enclosed in analysis chamber **106**. In embodiments in which members **12** and **16** are separated from each other, system **100** preferably comprises two cartridge holders **102** such that each of members **12** and **16** is loaded separately into system **100**. While, for clarity of presentation FIGs. 4-7 show only one cartridge holder, one of ordinary skills in the art, provided with the details described herein would know how to adjust system **100** to the case in which each of members **12** and **16** is loaded into a separate cartridge holder.

System **100** can also comprise a robotic arm system **108** carrying a pipette **110** having a disposable tip **111**. Pipette **110** can be a controllable air displacement pipette, as known in the art,

and tip **111** can be detachable from pipette **110**. System **100** further comprises a controller **112** configured for controlling robotic arm system **108** to establish a relative motion between device **10** and pipette **110** such that tip **111** of pipette **110** sequentially visits at least cartridge device **10** and analysis chamber **106**. Controller **112** optionally and preferably ensures that pipette **110** connects to, and picks up, one of the tips **111** in compartment **20** of device **10** (see FIG. 1D) before visiting wells **14** and container **40** or chamber **30**, and further ensures that pipette **110** releases tip **111** into compartment **20**, after visiting analysis chamber **106**. Controller **112** optionally also configured to control pipette **110** (*e.g.*, by controlling piston motions within pipette **110**) to aspirate liquids into tip **111** and/or dispense liquid out of tip **111**. Controller **112** optionally and preferably receives signals from a data processor **113**. Preferably, but not necessarily, both controller **112** and data processor **113** are mounted on the same control board **138**.

System **100** optionally and preferably comprises a display **114** for displaying information thereon. For example, display **114** can receive display instructions from internal analyzer system **104** to display the results of the analysis performed by internal analyzer system **104**. In some embodiments of the present invention, system **100** comprises a reader device **136** for reading information stored on device **10**, for example, by means of identifier **34** (not shown, see, *e.g.*, FIG. 1A). Reader device **136** is compatible with the type of storage on device **10**. For example, when device **10** comprises an identifier in the form of a barcode, reader device **136** can be embodied as an optical barcode reader device, and when device **10** comprises an identifier in the form of an electronic chip, *e.g.*, an RFID chip, reader device **136** can be embodied as an RFID reader device.

In some embodiments of the present invention system **100** employs an analysis protocol based on the information read by reader device **136**, for example, by selecting a protocol from a list of protocols recorded on a computer readable medium accessible by data processor **113**. Alternatively, the list of protocols can be recorded on an external computer readable medium, in which case the information read by reader device **136** is optionally and preferably transferred over a network to an external computer (not shown), that selects the protocol from the list of protocols and transfers it to system **100**. The protocol to be run by system **100** may comprise instructions to controller **112** to perform the protocol, including but not limited to a particular assay to be run and a detection method to be performed.

In some embodiments of the present invention, system **100** comprises a magnet **150**, for applying a magnetic field. The magnet **150** can be a permanent magnet or an electromagnet, as desired. Magnet **150** is particularly useful when wells **14** of device **10** comprise one or more

wells containing an antibody that is immobilized on a solid magnetic carrier. The magnetic field generated by magnet **150** can then be used for separating the target substance from other components in tip **111** of pipette **110**, as further detailed hereinabove.

In some embodiments of the invention there is more than one magnet which performs part or all the task of separating the target substance from other components in tip **111**.

A partial laid-open view of system **100**, illustrating cartridge holder **102** according to some embodiments of the present invention is provided in FIG. 5A. As shown, in these embodiments cartridge holder **102** comprises a lever system **116** for automatically hinging the second member **16** of device **10**, when cartridge holder **102** receives device **10**. In embodiments in which the first and second members of device **10** are slideably connected, lever system **116** is configured for automatically sliding the second member over the first member and hinging the second member. Lever system **116** is preferably controlled by controller **112**, automatically upon receipt of device **10** by holder **102**. In some embodiments of the present invention, controller **112** controls lever system **116** to draw device **10** inwardly along directing **118** prior to the hinging of second member **16**. A recess **120** is optionally and preferably also provided for fixing second member **16** in its vertical position after member **16** is hinged by level system **116**. Once cartridge device **10** is in its position, controller **112** preferably controls lever system **116** to disengage from device **10**, for example, upward and forward along direction **122**.

In some embodiments of the present invention system **100** comprises a heating system **124**. Heating system **124** can be of any type. The heating system can be configured to heat the cartridge by conduction, radiation and/or convection. In some embodiments of the present invention the heating system heats the cartridge device by conduction. Alternatively, the heating system heats the cartridge device by radiation or convection but without conduction.

In some embodiments of the present invention system **124** comprises a resistive heating element **128**. When resistive heating is employed, heating system **124** is preferably position below device **10** and in thermal communication therewith. Preferably, heating system **124** comprises a stage **126** configured to automatically engage cartridge device **10** from below once cartridge device **10** is its place. This can be done in more than one way.

For example, in one embodiment, illustrated in FIGs. 5B-C, a cam **130** and a roller **132** are employed to raise heating element **128**. In these embodiments, heating system **124** can also facilitates the alignment of cartridge device **10**, in which case cam **130** also engages a datum feature **134** into member **16** for better alignment. FIG. 5C illustrates an exploded view of heating system **124**.

In other embodiments, illustrated in FIGs. 5D-G, stage **126** is biased upwards by a spring (not shown) but is held at a lower position by cam **130**. Once cartridge device **10** is received, cam **130** is pushed by device **10** and releases stage **126** to move upwards. FIGs. 5E-G illustrate the position of stage **126** before (FIG. 5E), during (FIG. 5F) and after the completion (FIG. 5G) of the motion of cam **130**.

An additional partial laid-open view of system **100**, illustrating robotic arm system **108** according to some embodiments of the present invention is provided in FIGs. 6A-C. Shown are three orthogonal Cartesian axes X, Y and Z of motion, where Z is along the vertical direction. In some embodiments of the present invention robotic arm system **108** is configured to move pipette **110** along a planar path in the Y-Z plane, and to move holder **102** linearly, and optionally reciprocally, along the X axis. These embodiments are illustrated in FIGs. 6A and 6B. In alternative embodiments of the present invention, robotic arm system **108** is configured to move pipette **110** along a planar path in the X-Z plane, and to move holder **102** linearly, and optionally reciprocally, along the Y axis. These embodiments are illustrated in FIG. 6C. In any event, the motion of robotic arm system **108** is preferably selected to allow tip **111** of pipette **110** to visit each of wells **14** of device **10**, to visit compartment **20** of member **16**, to visit analysis chamber **106**, and to visit at least one of container **40** (when loaded into cavity **32** of device **10**) and chamber **30** (when containing the liquid). When compartment **20** is partitioned into partitions **28**, controller **112** is preferably configured for controlling robotic arm system **108** to pick up different pipette tips from different partitions and to correspondingly release different pipette tips into different partitions.

In embodiments in which cartridge device **10** comprises a waste collecting chamber **24**, controller **112** of system **100** is preferably configured for controlling robotic arm system **108** to visit also waste collecting chamber **24**, after visiting analysis chamber **106**. In embodiments in which container **40** is placed in cavity **32** of cartridge device **10**, controller **112** is configured for controlling robotic arm system **108** to visit container **40**. When container **40** and/or cartridge device **10** comprises a pierceable film, controller **112** is preferably configured for controlling robotic arm system **108** to pierce the film by tip **111** of pipette **110**.

FIG. 7 is a schematic illustration showing an exploded view of internal analyzer system **104**, according to some embodiments of the present invention. Preferably, analysis chamber **106** is a dark chamber and internal analyzer system **104** is an optical analyzer configured for detecting chemiluminescent signals from the pipette tip **111** (not shown in FIG. 7) when the pipette tip is in dark chamber **106**. In the illustrated embodiment, dark chamber **106** is tubular and is held by a tube holder **140**. An optical detector **142** such as, but not limited to, a photomultiplier tube

(PMT) is mounted on a side wall of camber **106** by means of a mount structure **144** having an opening **146** for optical signal to propagate from chamber **106** through opening **146** and into optical detector **142**. A sealing ring **148** is optionally and preferably introduced at opening **146** for preventing stray light from entering optical detector **142**.

It was found by the inventors that the detection sensitivity varies with the variation of the position of the tip of the pipette within chamber **106**, and particularly variations in the distance of the tip from the optical detector **142**. FIGs. 8A-C are schematic illustrations of a cross-section along a horizontal plane of internal analyzer system **104**, once assembled. Also shown, are three different horizontal positions of the tip **111** of pipette **110** once introduced into chamber **106**. The distance between the tip **111** of pipette **110** and optical detector **142** is marked in FIGs. 8A-C by ΔX. FIGs. 8A-C correspond to three different values of ΔX, *e.g.*, about 5 mm in FIG. 8A, about 10 mm in FIG. 8B, and about 15 mm in FIG. 8C.

FIG. 9 is a graph showing the detected optical signal as the pipette tip moves vertically (along the Z direction) at a constant horizontal position, as obtained in experiments performed according to some embodiments of the present invention using a PMT purchased from Hamamatsu Photonics K.K. Each curve in FIG. 9 corresponds to a different (constant) value of ΔX, where the actual distance from the sensor in the optical detector is about $8+\Delta X$ mm. A maximum attenuation of about 3.5 was observed. For a PMT purchased from ET Enterprises Ltd., smaller attenuation of 1.8 was observed since the detection window of Hamamatsu PMT is smaller than that on the ET PMT. As demonstrated in FIG. 9, the vertical position of the tip has a lesser impact than the horizontal position. The present Inventors also found that the detection is less sensitive to variations of the tip's horizontal position along the Y axis (perpendicularly to the optical axis of optical detector **142**).

The present inventors found that when the internal walls of chamber **106** are coated, at least partially, by a reflective coating, the sensitivity to the variation in the horizontal distance between the tip and the optical detector is reduced.

The reflective coating can be, for example, an aluminum foil (optionally and preferably its matt side), a paper reflective coating, a metallic reflective coating. The reflective coating may be deposed onto the inner wall of chamber **106** by any technique known in the art including, without limitation, thermal disposition or vapor disposition, plating and the like. The reflective coating can also be in the form of a foil or leaf. The reflective coating may optionally and preferably be polished after application, or may be applied in a manner that produces a high degree of reflection without the need for polishing. A protective layer may optionally and preferably be formed or deposited to overly the reflective coating. For example, a protective oxide dielectric

coating may be formed, for example using techniques commonly employed to form passivation layers in silicon fabrication processes. The oxide may provide environmental protection to the underlying reflective coating. The oxide may additionally or alternatively serve as a filter, ensuring reflection of certain defined wavelengths or ranges of wavelengths, while reducing or eliminating the reflection of other wavelengths or ranges of wavelengths. Thus, wavelengths which are not of interest may be advantageously suppressed.

FIG. 10 is a graph showing an intensity decay as a function of ΔX, where the actual distance from the sensor in the optical detector is about $8+\Delta X$ mm, as obtained during experiments performed according to some embodiments of the present invention using a matt side of an aluminum foil (designated "MattAllie" in FIG. 10) reflective coating, a paper reflective coating, and no reflective coating (control). As shown the intensity curves are considerably shallower with the reflective coating than without the reflective coating. Since the sensitivity is directly proportional to the gradient of these curves, FIG. 10 demonstrates that the use of reflective coating reduces the positional accuracy required the robotic arm system **108**.

While the dark chamber **106** can have any shape or form, certain shapes that enhance reflection toward the optical detector **142** are preferred. Preferably, an interior of the dark chamber **106** has a physical form capable of reflecting or otherwise directing at least a portion of the photons generated by the reaction within the pipette tip towards optical detector **142**. Such reflection can be accomplished using one or more concave inner surfaces as the internal wall of the dark chamber **106**. In at least some instances, the concave inner surface can be generally oval or cylindrical, for example as shown in FIG. 7. Also contemplated are embodiments in which the inner wall of dark chamber **106** are generally spherical or hemispherical.

A representative operation procedure of system **100** will now be described with reference to FIGs. 11A-C. Cartridge device **10**, with wells filled with substances for performing the assay, with sterile disposable tips placed within compartment **20** of hinged second member **16**, and with container **40** placed within cavity **32**, is introduced by the operator **160** to holder **102** (FIG. 11A), wherein container **40** already contains the liquid (*e.g.*, body liquid). Alternatively, instead of container **40** within cavity **32**, chamber **30** can include a liquid (*e.g.*, body liquid) as further detailed hereinabove. Still alternatively, device **10** can be loaded with two types of liquids one type in container **40** and another type in chamber **30**. A non-limiting example includes a scenario in which a capillary blood sample is introduced into container **40** which is then loaded into cavity **32** of device **10** to allow measurements of host (patient) proteins, and a nasal mucus sample (collected by a nasal swab) is introduced into chamber **30** of the same device **10** to allow measurements of presence, absence or level of micro-organism (*e.g.*, bacteria, virus, fungi)

related proteins, for example hemagglutinin and neuraminidase of the influenza virus. In this specific exemplary embodiment, device **10** is used to monitor both the host response to a potential infection and to detect or quantify the presence of a disease causing agent. The wells can contain an antibody that is immobilized to the solid magnetic carrier, a labeled antibody, and a wash buffer.

Cartridge device **10** is then pushed forward into system **100** (FIG. 11B), optionally and preferably until an acoustic indication (*e.g.*, a click) or mechanical detent is effected to indicate that the cartridge device **10** is properly inserted. Lever system **116** (not shown, see FIG. 5A) draws cartridge device **10** further inwards and hinges the second member **16** (not shown in FIGs. 11A-C, see FIGs. 5A-B) of device **10**. Heating system **124** engages the bottom of device **10** as further detailed hereinabove.

Optionally, the robotic arm picks up one of tips from the tip container by way of driving the robotic arm mandrel into one of the tips in the container, which causes the tip to expand and attach to the robotic arm by friction. The robotic arm then maneuvers the tip such that it leaved container without any obstacles.

Optionally, the information on identifier **34** (not shown) is read by reader **136**. Controller **112** establishes a relative motion between device **10** and pipette **110** such that pipette **110** visits compartment **20** and connects to one of the new tips in compartment **20** (not shown in FIGs. 11A-C, see FIGs. 1A, 1B, 1D, 5A and 5B). Controller **112** then establishes a relative motion between device **10** and pipette **110** such that pipette **110** aspirates into tip **111** the liquid (either from container **40** or from chamber **30**), as well as the antibody that is immobilized to the solid magnetic carrier, by visiting container **40** or chamber **30** and the respective wells. Controller **112** also ensure that pipette **110** aspirates into tip **111** the wash buffer from the respective well, and moves the pipette **110** such that tip **111** is proximate to magnet **150** (not shown, see FIG. 4). The magnetic field generated by magnet **150** separates the solid magnetic carrier thereby also the target substance from other components in tip **111** of pipette **110**, wherein the solid magnetic carrier is concentrated at the side wall of tip **111** of pipette **110**. While the solid magnetic carrier is at the side wall, controller **112** causes pipette **110** to release into the waste collection chamber of device **10** the wash buffer from tip **111**, including any component that is not immobilized to the magnetic carrier.

According to some embodiments of the invention, two magnets can be used to achieve the separation of the target substance from other materials. One magnet can be used to attract the solid carrier into the tip wall, and another magnet can then be employed to change the magnetic

field such that when the pipette is releasing the waste material, the target substance is retained with greater efficacy than achievable with the magnetic field used for attracting the solid carrier.

Controller **112** then causes pipette **110** to aspirate into tip **111** the labeled antibody from the respective well. The labeled antibody binds to the target substance on the magnetic carrier. Controller **112** can then optionally and preferably move tip **111** of pipette **110** into a well that contains inhibitory solution, for contacting the outer walls of tip **111** by the inhibitory solution. Preferably, the inhibitory solution does not enter the tip. This can be ensured by not operating pipette **110** to aspirate the inhibitory solution into tip **111**.

Controller **112** moves tip **111** of pipette **110** into chamber **106** for analysis by internal analyzer system **104**, which optionally and preferably uses processor **113** for the analysis. For example, processor **113** can receive signals from the optical detector of system **104** and determine the existence, absence, or level of the target substance in the liquid (*e.g.*, body liquid) based on the intensity of the signals.

When the outer walls of tip **111** is contacted with the inhibitory solution, of tip **111** preferably enters into chamber **106** immediately after said contact. It was surprisingly found by the Inventors that such a procedure significantly reduces the possibility of non-specific enzyme activity.

Once the analysis is completed, controller **112** establishes a relative motion between device **10** and pipette **110** until tip **111** of pipette **110** enters compartment **20** of hinged second member **16** (not shown in FIGs. 11A-C, see FIGs. 1A, 1D, 5A and 5B) of device **10**. Controller **112** releases tip **111** of pipette **110** into compartment **20**.

Optionally in some embodiments of the invention, the tip is released by the way of the robot, after having placed tip in the designated location within compartment **20**, then moves up through either a fixed or moving mechanical fork-like structure which is narrower than the width of the tip, but wider than the width of the robotic arm mandrel. The tip is then forced away from the mandrel, and the tip is then released when the robotic arm continues the motion through the mechanical fork-like structure.

Optionally and preferably, controller **112** causes robotic arm **108** to pick up another new pipette tip from compartment **20** and performs another assay by repeating the above operations protocol with another set of wells of the same cartridge. Processor **113** can instruct the display **114** to display the results obtained from one or more of the performed assays.

Optionally and preferably, the system has a door mechanism which is opened when a cartridge needs to be loaded into the system, and when a cartridge is ejected from the device. In

all other times, the door is closed which prevents operators' access to the internal components of the analyzer.

In some embodiments of the present invention device **10** and system **100** are subjected to a calibration and testing procedure. A calibrating liquid and auxiliary liquids for testing the cartridge device **10** and system **100** are stored in a dropper and put into the cartridge device **10** with drops to circumvent use of pipette. Vials with calibrating liquids can be stored within a vial with a nozzle. The operator can tip the vial nozzle into the sample chamber **30**, and apply a predetermined number of drops into sample chamber **30**. The inventors found that this reduces the possibility of bubble formation when dispensing the calibrator fluid into the sample well.

According to some embodiments of system **100** has dimensions of Xcm×Ycm×Zcm, wherein each of X, Y and Z is from about 75 to about 125, e.g., about 100. According to some embodiments of the system has dimensions of Xcm×Ycm×Zcm, wherein each of X, Y and Z is from about 35 to about 65, e.g., about 50. According to some embodiments of the system has dimensions of Xcm×Ycm×Zcm, wherein each of X, Y and Z is from about 16 to about 30, e.g., about 23. According to some embodiments of the system has dimensions of Xcm×Ycm×Zcm, wherein each of X and Y is from about 20 to about 26, e.g., about 23, and wherein Z is from about 26 to about 34, e.g., about 30.

As used herein the term “about” refers to ± 10 %.

The word "exemplary" is used herein to mean "serving as an example, instance or illustration." Any embodiment described as "exemplary" is not necessarily to be construed as preferred or advantageous over other embodiments and/or to exclude the incorporation of features from other embodiments.

The word "optionally" is used herein to mean "is provided in some embodiments and not provided in other embodiments." Any particular embodiment of the invention may include a plurality of "optional" features unless such features conflict.

The terms "comprises", "comprising", "includes", "including", “having” and their conjugates mean "including but not limited to".

The term “consisting of” means “including and limited to”.

The term "consisting essentially of" means that the composition, method or structure may include additional ingredients, steps and/or parts, but only if the additional ingredients, steps and/or parts do not materially alter the basic and novel characteristics of the claimed composition, method or structure.

As used herein, the singular form "a", "an" and "the" include plural references unless the context clearly dictates otherwise. For example, the term "a compound" or "at least one compound" may include a plurality of compounds, including mixtures thereof.

Throughout this application, various embodiments of this invention may be presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the invention. Accordingly, the description of a range should be considered to have specifically disclosed all the possible subranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed subranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 3, 4, 5, and 6. This applies regardless of the breadth of the range.

Whenever a numerical range is indicated herein, it is meant to include any cited numeral (fractional or integral) within the indicated range. The phrases “ranging/ranges between” a first indicate number and a second indicate number and “ranging/ranges from” a first indicate number “to” a second indicate number are used herein interchangeably and are meant to include the first and second indicated numbers and all the fractional and integral numerals therebetween.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination or as suitable in any other described embodiment of the invention. Certain features described in the context of various embodiments are not to be considered essential features of those embodiments, unless the embodiment is inoperative without those elements.

ANNEX

It will be appreciated that the protein names presented herein are given by way of example. Many alternative names, aliases, modifications, isoforms and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all the alternative protein names, aliases, modifications isoforms and variations.

Gene products, are identified based on the official letter abbreviation or gene symbol assigned by the international Human Genome Organization Naming Committee (HGNC) and listed at the date of this filing at the US National Center for Biotechnology Information (NCBI) web site also known as Entrez Gene.

TRAIL: The protein, TNF Related Apoptosis Inducing Ligand (TRAIL), encoded by this gene is a cytokine that belongs to the tumor necrosis factor (TNF) ligand family. Additional names of the gene include without limitations APO2L, TNF-related apoptosis-inducing ligand, TNFSF10 and CD253. TRAIL exists in a membrane bound form and a soluble form, both of which can induce apoptosis in different cells, such as transformed tumor cells. This protein binds to several members of the TNF receptor superfamily such as TNFRSF10A/TRAILR1, NFRSF10B/TRAILR2, NFRSF10C/TRAILR3, TNFRSF10D/TRAILR4, and possibly also to NFRSF11B/OPG. The activity of this protein may be modulated by binding to the decoy receptors such as NFRSF10C/TRAILR3, TNFRSF10D/TRAILR4, and NFRSF11B/OPG that cannot induce apoptosis. The binding of this protein to its receptors has been shown to trigger the activation of MAPK8/JNK, caspase 8, and caspase 3. Alternatively spliced transcript variants encoding different isoforms have been found for this gene. TRAIL can be proteolytically cleaved from the cell surface to produce a soluble form that has a homotrimeric structure.

According to some embodiments, at least one of wells **14** contains an antibody that binds with the soluble (i.e. secreted) form of TRAIL.

According to some embodiments, at least one of wells **14** contains an antibody that binds with the membrane form of TRAIL is measured.

According to some embodiments, at least one of wells **14** contains an antibody that binds with the membrane form of TRAIL and at least one of wells **14** contains an antibody that binds with the secreted form of TRAIL.

IP10: This gene encodes a chemokine of the CXC subfamily and ligand for the receptor CXCR3. Binding of this protein to CXCR3 results in pleiotropic effects, including stimulation of monocytes, natural killer and T-cell migration, and modulation of adhesion molecule expression. Additional names of the gene include without limitations: IP-10, CXCL10, Gamma-IP10, INP10 and chemokine (C-X-C motif) ligand 10.

CRP: C-reactive protein; additional aliases of CRP include without limitation RP11-419N10.4 and PTX1. The protein encoded by this gene belongs to the pentaxin family. It is involved in several host defense related functions based on its ability to recognize foreign pathogens and damaged cells of the host and to initiate their elimination by interacting with humoral and cellular effector systems in the blood. Consequently, the level of this protein in plasma increases greatly during acute phase response to tissue injury, infection, or other inflammatory stimuli. CRP displays several functions associated with host defense: it promotes agglutination, bacterial capsular swelling, phagocytosis and complement fixation through its calcium-dependent binding to phosphorylcholine.

IL1RA: The protein encoded by this gene is a cytokine receptor that belongs to the interleukin 1 receptor family. This protein is a receptor for interleukin alpha (IL1A), interleukin beta (IL1B), and interleukin 1 receptor, type I (IL1R1/IL1RA). It is an important mediator involved in many cytokine induced immune and inflammatory responses. Additional names of the gene include without limitations: CD121A, IL-1RT1, p80, CD121a antigen, CD121A, IL1R and IL1ra.

PCT: Procalcitonin (PCT) is a peptide precursor of the hormone calcitonin, the latter being involved with calcium homeostasis. Procalcitonin ("pCT") is a protein consisting of 116 amino acids and having a molecular weight of about 13,000 dalton. It is the prohormone of calcitonin which under normal metabolic conditions is produced and secreted by the C cells of the thyroid. pCT and calcitonin synthesis is initiated by translation of preprocalcitonin ("pre-pCT"), a precursor peptide comprising 141 amino acids. The amino acid sequence of human pre-pCT was described by Moullec et al. in FEBS Letters, 167:93-97 in 1984. pCT is formed after cleavage of the signal peptide (first 25 amino acids of pre-pCT).

***SAA*:** encodes a member of the serum amyloid A family of apolipoproteins. The encoded protein is a major acute phase protein that is highly expressed in response to inflammation and tissue injury. This protein also plays an important role in HDL metabolism and cholesterol homeostasis. High levels of this protein are associated with chronic inflammatory diseases including atherosclerosis, rheumatoid arthritis, Alzheimer's disease and Crohn's disease. This protein may also be a potential biomarker for certain tumors. Alternate splicing results in multiple transcript variants that encode the same protein.

Although the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all such alternatives, modifications and variations that fall within the spirit and broad scope of the appended claims.

All publications, patents and patent applications mentioned in this specification are herein incorporated in their entirety by reference into the specification, to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein by reference. In addition, citation or identification of any reference in this application shall not be construed as an admission that such reference is available as prior art to the present invention. To the extent that section headings are used, they should not be construed as necessarily limiting.

WHAT IS CLAIMED IS:

1. A cartridge device for analyzing a body liquid, the cartridge comprising:

a first member having a plurality of wells for performing assays; and

a second member, connected to said first member, and having a compartment for holding at least one disposable pipette tip.

2. The device of claim 1, wherein said second member is hingedly connected to said first member.

3. The device of claim 1, wherein said second member is slideably connected to said first member.

4. The device according to claim 1, wherein said compartment of said second member is oriented for holding said at least one disposable pipette tip in a generally upright orientation.

5. The device according to any of claims 2-3, wherein said compartment of said second member is oriented for holding said at least one disposable pipette tip in a generally upright orientation.

6. A kit for analyzing a body liquid, the kit comprising:

a first member having a plurality of wells for performing assays; and

a second member, connectable to said first member, and having a compartment for holding at least one disposable pipette tip.

7. The device according claim 1, further comprising an openable or pierceable covering structure covering said wells.

8. The device or kit according to any of claims 2-6, further comprising an openable or pierceable covering structure covering said wells.

9. The device according to claim 1, further comprising a waste collecting chamber.

10. The device or kit according to any of claims 2-7, further comprising a waste collecting chamber.

11. The device or kit according to claim 9, wherein said waste collecting chamber comprises a moisture absorber.

12. The device or kit according to claim 10, wherein said waste collecting chamber comprises a moisture absorber.

13. The device according to claim 9, wherein said waste collecting chamber comprises a moisture absorber.

14. The device or kit according to claim 10, wherein said waste collecting chamber comprises a moisture absorber.

15. The device according to claim 9, wherein said waste collecting chamber is covered by a lid.

16. The device or kit according to claim 11, wherein said waste collecting chamber is covered by a lid.

17. The device or kit according to claim 9, wherein said waste collecting chamber is locked by a 1 way valve.

18. The device or kit according to any of claims 10-16, wherein said waste collecting chamber is locked by a 1 way valve.

19. The device according to claim 9, wherein said waste collecting chamber prevent liquid spillage using a direction structure.

20. The device or kit according to any of claims 10-18, wherein said waste collecting chamber prevent liquid spillage using a direction structure.

21. The device according to claim 9, wherein said waste collecting chamber is covered by a pierceable barrier.

22. The device or kit according to any of claims 10-20, wherein said waste collecting chamber is covered by a pierceable barrier.

23. The device according to claim 9, wherein said waste collecting chamber is covered by a lid connected to or being an extension of said second member, to be exposed when said second member is hinged in a generally upright orientation.

24. The device or kit according to any of claims 10-22, wherein said waste collecting chamber is covered by a lid connected to or being an extension of said second member, to be exposed when said second member is hinged in a generally upright orientation.

25. The device according to claim 9, wherein said waste collecting chamber is subdivided to sub-chambers.

26. The device or kit according to any of claims 10-24, wherein said waste collecting chamber is subdivided to sub-chambers.

27. The device according to claim 9, wherein said waste collecting chamber comprises more than one entry point.

28. The device or kit according to any of claims 10-26, wherein said waste collecting chamber comprises more than one entry point.

29. The device according to claim 9, wherein said waste collecting chamber extends to beneath said wells.

30. The device or kit according to any of claims 10-28, wherein said waste collecting chamber extends to beneath said wells.

31. The device according to claim 1, wherein said second member is partitioned into a plurality of partitions, each constituted for holding one pipette tip.

32. The device or kit according to any of claims 2-30, wherein said second member is partitioned into a plurality of partitions, each constituted for holding one pipette tip.

33. The device according to claim 31, wherein a number of said partitions equals at least a number of said assays.

34. The device according to claim 1, wherein said plurality of wells comprises at least one well containing a first antibody immobilized on a solid magnetic carrier, and at least one well containing a second antibody labeled with labeling substance, and wherein said antibodies are selected to specifically bind to a target substance in the body liquid.

35. The device or kit according to any of claims 2-33, wherein said plurality of wells comprises at least one well containing a first antibody immobilized on a solid magnetic carrier, and at least one well containing a second antibody labeled with labeling substance, and wherein said antibodies are selected to specifically bind to a target substance in the body liquid.

36. The device according to claim 34, wherein said labeling substance is an enzyme, and wherein said antibodies and said enzyme are selected for detecting said target substance by a sandwich ELISA test.

37. The device or kit according to claim 35, wherein said labeling substance is an enzyme, and wherein said antibodies and said enzyme are selected for detecting said target substance by a sandwich ELISA test.

38. The device or kit according to any of claims 34 and 36, wherein said antibodies are selected to specifically bind to a protein selected from the group consisting of TRAIL protein, CRP protein and IP-10 protein.

39. The device or kit according to any of claims 34 and 36, wherein said antibodies are selected to specifically bind to a protein selected from the group consisting of: PCT, IL-6, BNP, Troponin, Troponin I, Troponin T, High sensitive Troponin, High sensitive CRP, IL1RA, CKB, RSAD2, MX1, TREM-1, PTH and Ubiquitin C- terminal Hydrolase-L1 (UCH-L1).

40. The device according to claim 1, further comprising said at least one disposable pipette tip within said compartment.

41. The device or kit according to any of claims 2-39, further comprising said at least one disposable pipette tip within said compartment.

42. The device according to claim 40, wherein said at least one disposable pipette tip antibody immobilized to solid magnetic carriers in said disposable pipette tip.

43. The device or kit according to claim 41, wherein said at least one disposable pipette tip antibody immobilized to solid magnetic carriers in said disposable pipette tip.

44. The device according to claim 1, wherein said first or second member comprises a cavity constituted for receiving and fittedly holding a container containing the body liquid.

45. The device or kit according to any of claims 2-40, wherein said first or second member comprises a cavity constituted for receiving and fittedly holding a container containing the body liquid.

46. A cartridge device for analyzing a body liquid, the cartridge comprising:

a first plurality of wells, each having a tapered base; and

a second plurality of wells, each having a non-tapered base;

wherein said first and said second plurality of wells are both formed in a monolithic structure.

47. The cartridge device according to claim 46, wherein at least one well of said a first plurality of wells contains a reagent.

48. The cartridge device according to claim 46, wherein at least one well of said a second plurality of wells is marked for containing a body liquid.

49. A kit for analyzing a body liquid, the kit comprising, in separate packaging, the device of any of claims 44 and 47 and said container.

50. The kit of claim 49, wherein said container has a volume of from about 5 µl to about 500 µl.

51. The kit of claim 49, wherein said container has a volume of from about 5 µl to about 500 µl.

52. The kit according to any of claims 49 and 50, wherein said container can be attached to a flat base.

53. The kit according to any of claims 49 and 50, wherein said container comprises a lid.

54. The kit according to claim 53, wherein said lid is foldable.

55. The kit according to any of claims 53 and 54, wherein said lid is pierceable.

56. The kit according to any of claims 53-55, wherein said lid seals said container.

57. The kit according to any of claims 49-55, wherein said container is transparent to visible light.

58. The kit according to any of claims 49-57, wherein an inner wall of said container is at least partially coated with an anticoagulant.

59. A system for analyzing a body liquid, the system comprising:

a cartridge holder, adapted for receiving the cartridge device according to claim 1;

an internal analyzer system having an analysis chamber, and being configured for analyzing the body liquid when enclosed in said analysis chamber;

a robotic arm system carrying a pipette; and

a controller configured for controlling said robotic arm system to establish a relative motion between said cartridge device and said pipette such that said pipette visits at least said tip compartment, picks up a tip from said compartment, visits cartridge device, said analysis chamber, and said compartment, and releases a tip of said pipette back into said compartment.

60. A system for analyzing a body liquid, the system comprising:

a cartridge holder, adapted for receiving the cartridge device or kit according to any of claims 2-44;

an internal analyzer system having an analysis chamber, and being configured for analyzing the body liquid when enclosed in said analysis chamber;

a robotic arm system carrying a pipette; and

a controller configured for controlling said robotic arm system to establish a relative motion between said cartridge device and said pipette such that said pipette visits at least said tip compartment, picks up a tip from said compartment, visits cartridge device, said analysis chamber, and said compartment, and releases a tip of said pipette back into said compartment.

61. The system of claim 59, further comprising a lever system for automatically hinging said second member responsively to said receiving.

62. The system of claim 60, further comprising a lever system for automatically hinging said second member responsively to said receiving.

63. A system for analyzing a body liquid, the system comprising:

a first cartridge holder, adapted for receiving a first cartridge member having a plurality of wells for performing assays;

a second cartridge holder, adapted for receiving a second cartridge member having a compartment for holding at least one disposable pipette tip;

an internal analyzer system having an analysis chamber, and being configured for analyzing the body liquid when enclosed in said analysis chamber;

a robotic arm system carrying a pipette; and

a controller configured for controlling said robotic arm system to establish a relative motion between said cartridge members and said pipette such that said pipette visits at least said tip compartment, picks up a tip from said compartment, visits said wells, said analysis chamber, and releases a tip of said pipette back into said compartment.

64. The system according to any of claims 59-63, wherein said cartridge device comprises a pierceable film covering said wells, and said controller is configured for controlling said robotic arm system to pierce said film while visiting said cartridge device.

65. The system according to any of claims 59 and 64, wherein said cartridge device comprises a waste collecting chamber, and wherein said controller is configured for controlling said robotic arm system to visit said waste collecting chamber.

66. The system according to any of claims 59-65, wherein said second member is partitioned into a plurality of partitions, and said controller is configured for controlling said robotic arm system to pick up and release different pipette tips into different partitions.

67. The system according to any of claims 59-66, wherein said first member comprises a cavity constituted for receiving and fittedly holding a container containing the body liquid, and wherein said controller is configured for controlling said robotic arm system to visit said container.

68. The system according to any of claims 59-67, wherein said plurality of wells comprises at least one well containing a first antibody immobilized on a solid magnetic carrier, and at least one well containing a second antibody labeled with labeling substance, said antibodies being selected to specifically bind to a target substance in the body liquid, wherein said a controller is configured for establishing said relative motion such that said pipette aspirates the body liquid, said immobilized first antibody and said labeled second antibody into said tip, and wherein the system comprises a magnetic system constituted for separating said solid magnetic carrier, thereby also said target substance, from other components in said tip.

69. The system according to any of claims 59-68, further comprising a heating system.

70. The system according to claim 69, wherein said heating system comprises a stage configured to automatically interface with said cartridge device responsively to said receiving of said cartridge device.

71. The system according to any of claims 59-70, wherein said analysis chamber is a dark chamber and said analyzer system is an optical analyzer configured for detecting chemiluminescent signals from said pipette tip when said pipette tip is in said dark chamber.

72. The system according to claim 71, wherein an inner wall of said dark chamber is at least partially coated by a reflective coating.

73. A method of analyzing a body liquid, the method comprising providing a pipette tip containing the body liquid, and an antibody conjugated to an enzyme and a substrate generating chemiluminescence signal during reaction of said body liquid with said antibody within said tip, and

operating an optical analyzer to detect said chemiluminescent signal from said pipette tip.

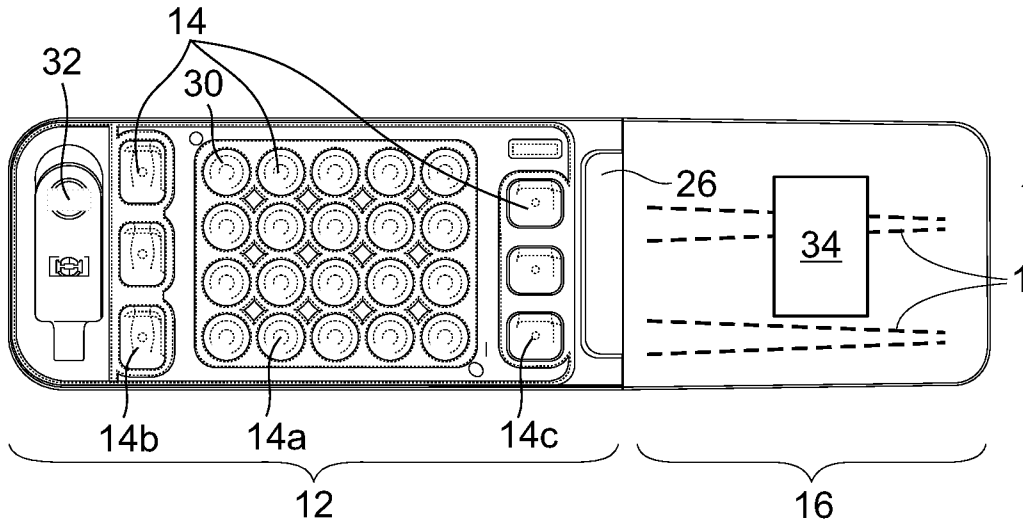

FIG. 1A

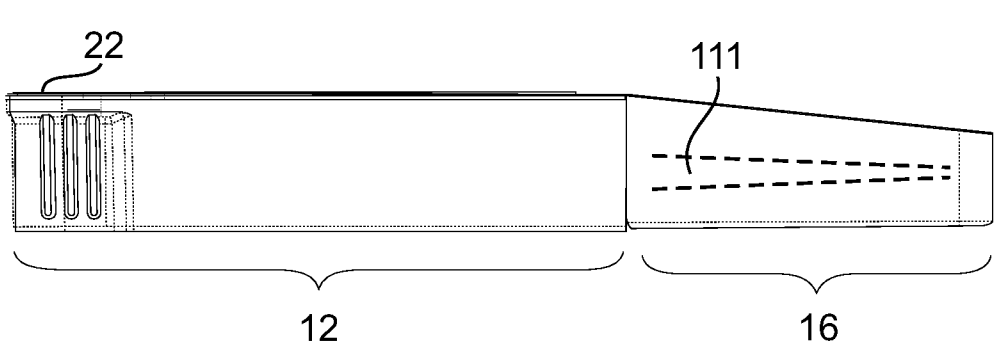

FIG. 1B

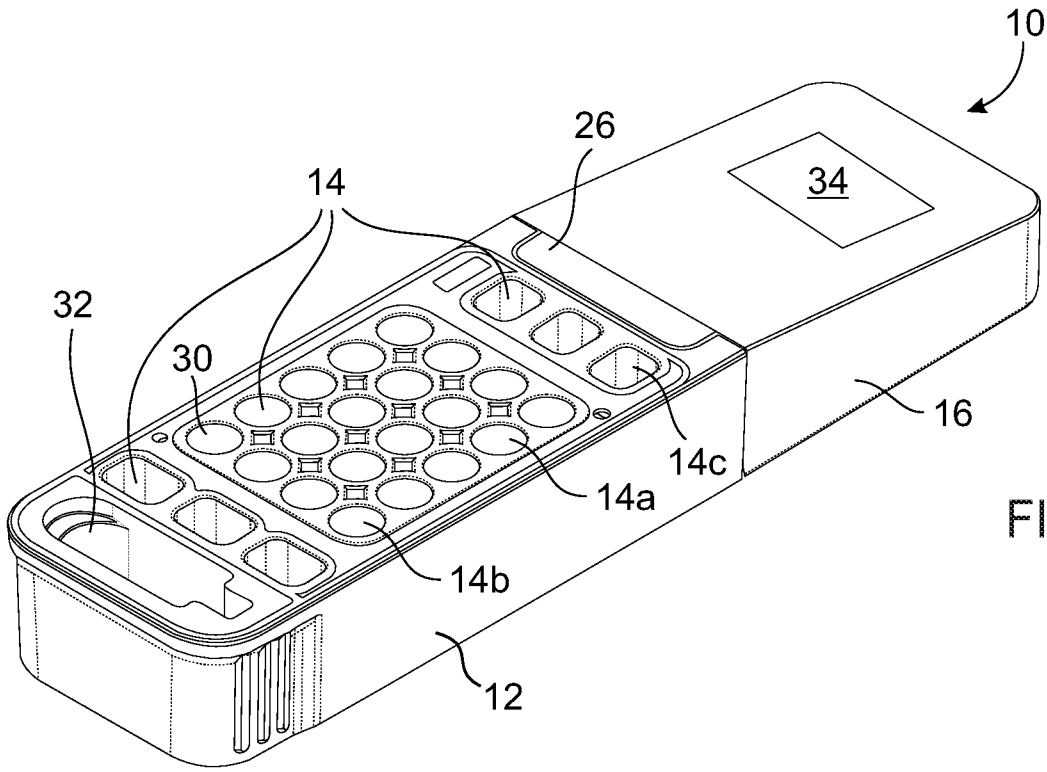

FIG. 1C

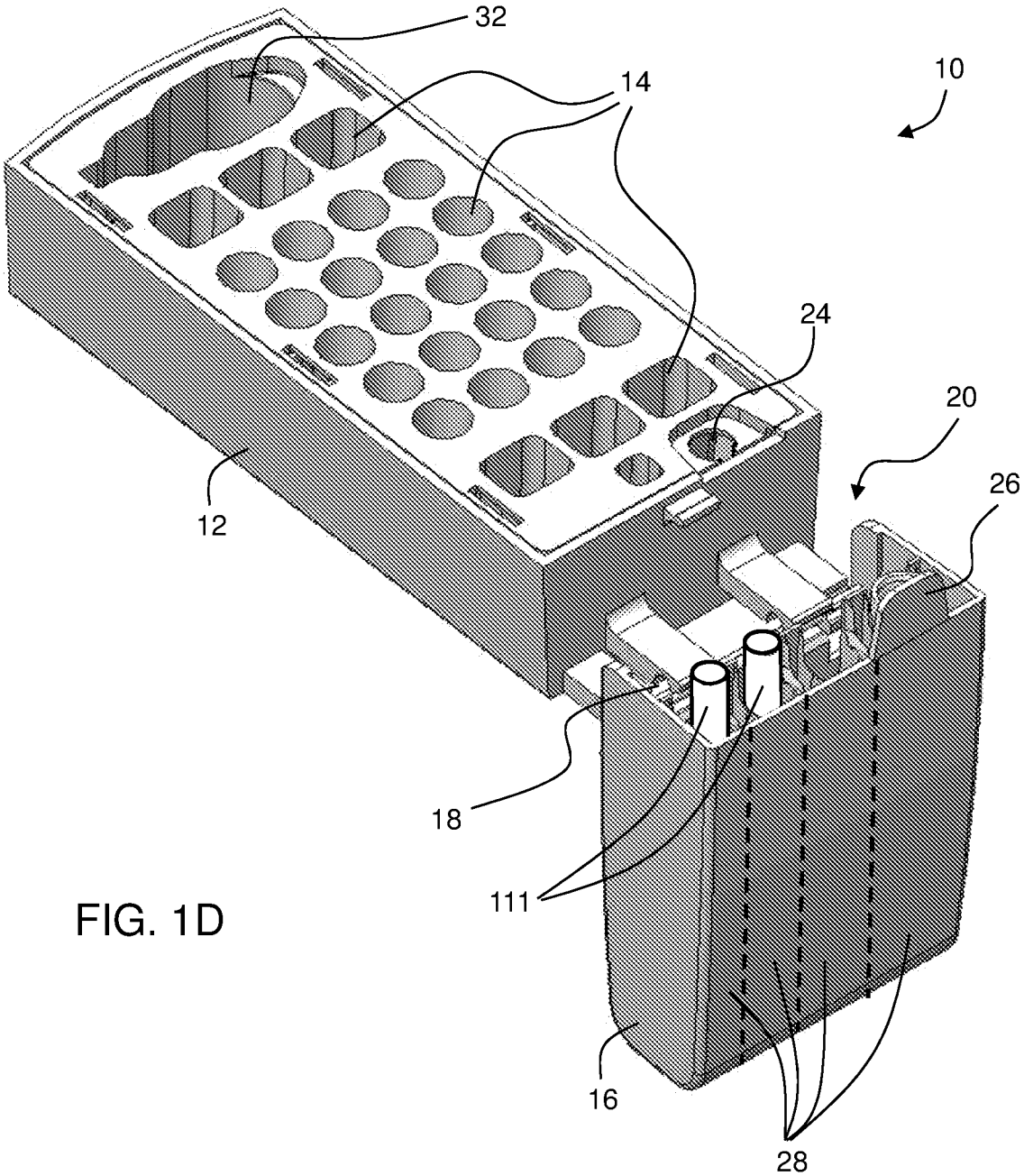

FIG. 1D

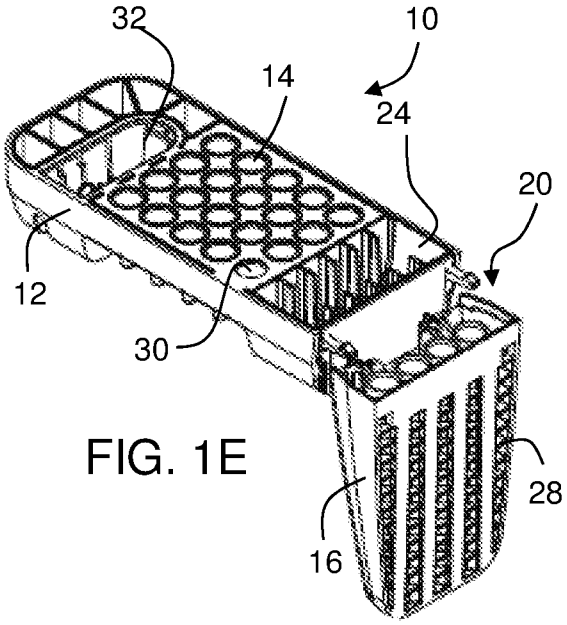

FIG. 1E

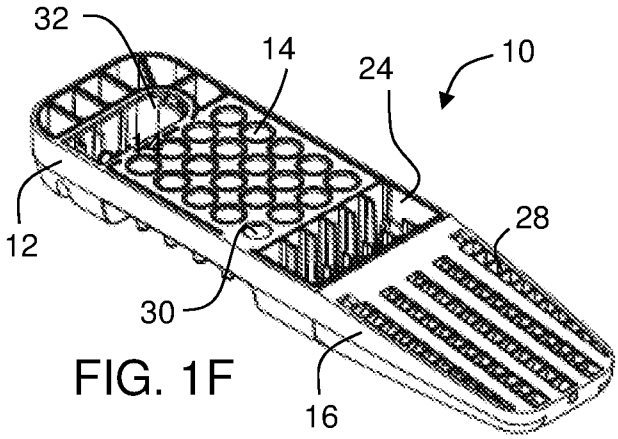

FIG. 1F

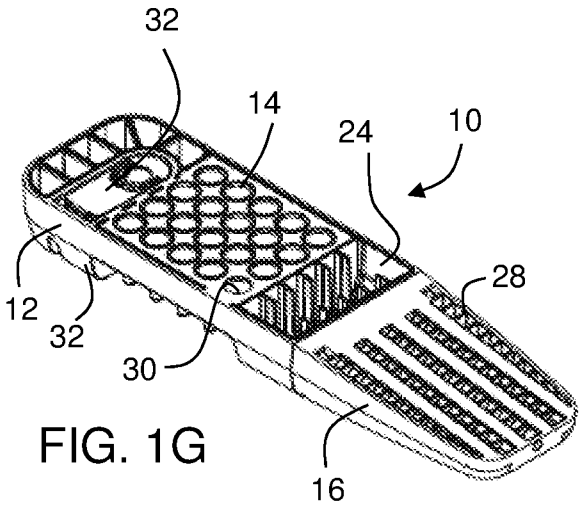

FIG. 1G

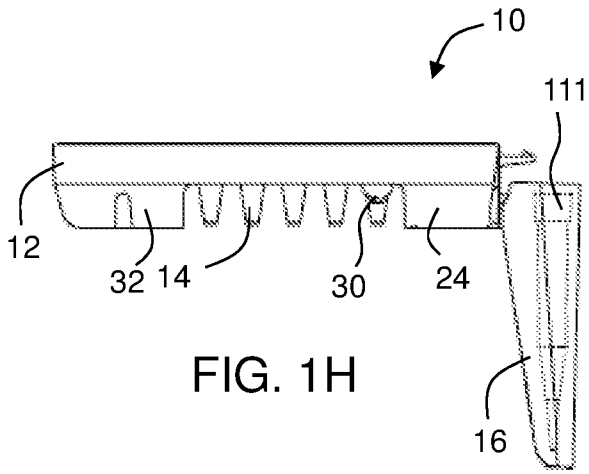

FIG. 1H

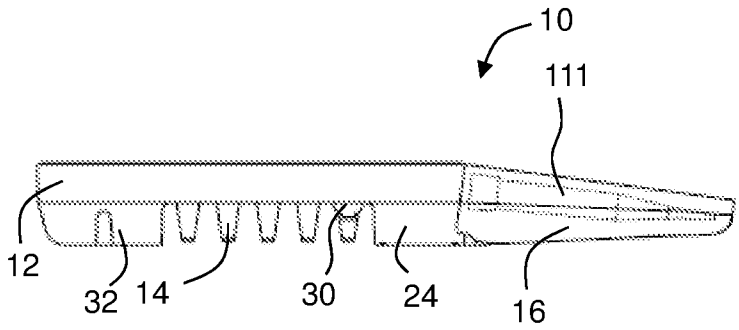

FIG. 1I

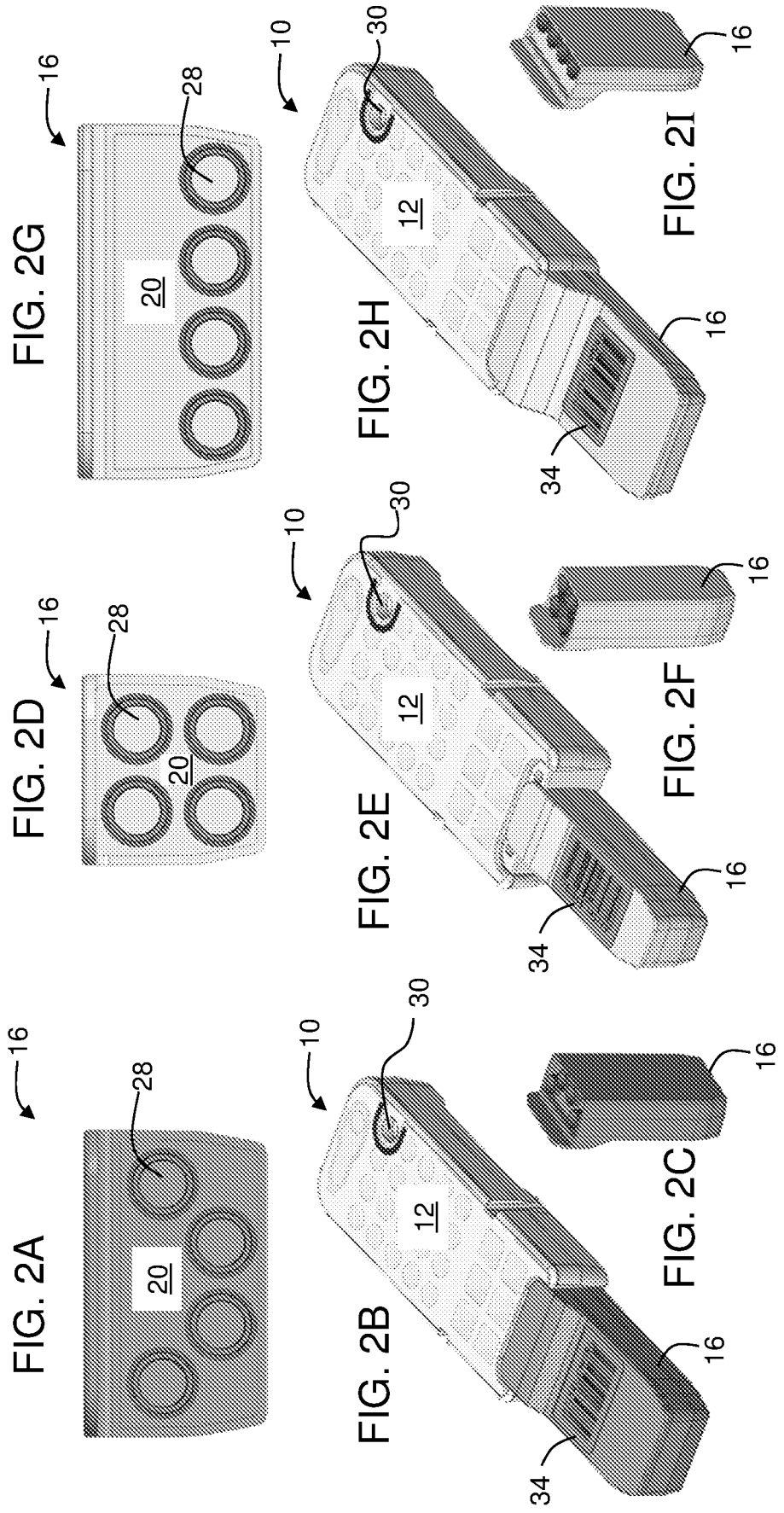
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FIG. 2A
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FIG. 2B
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FIG. 2C
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FIG. 2D
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FIG. 2E
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FIG. 2F
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FIG. 2G
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FIG. 2H
16
FIG. 2I

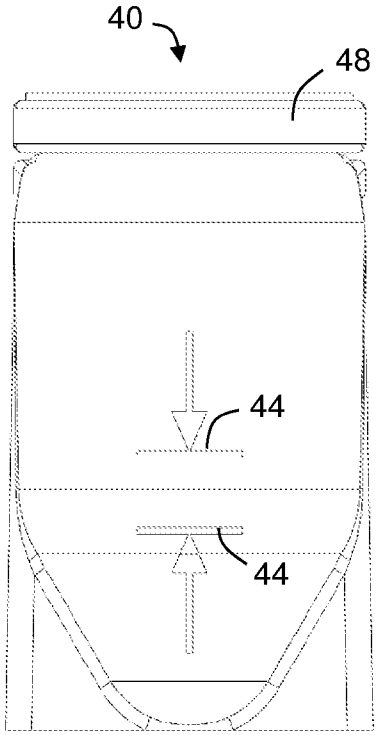


FIG. 3A

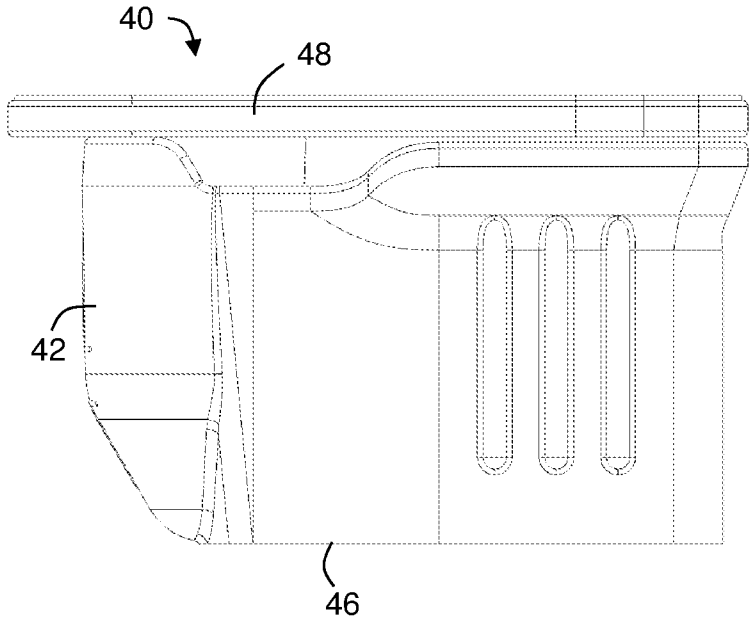


FIG. 3B

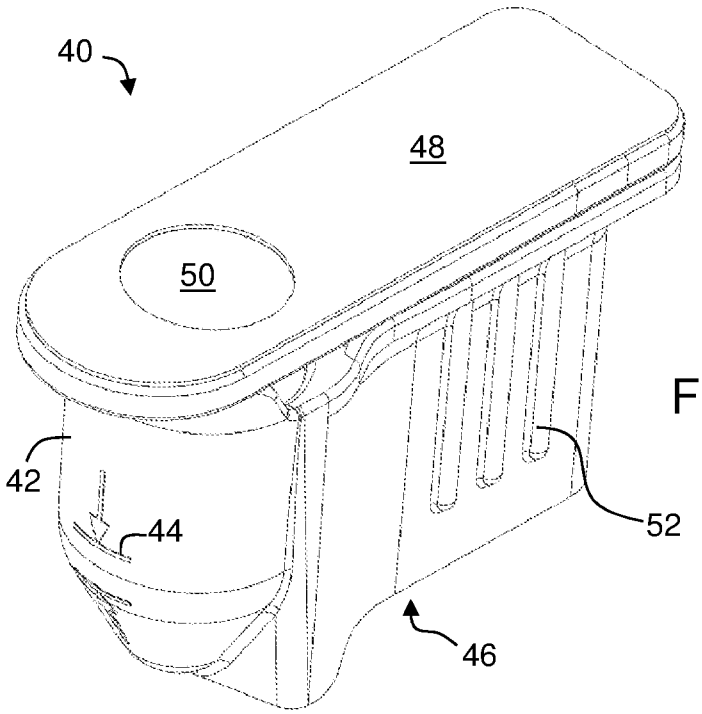


FIG. 3C

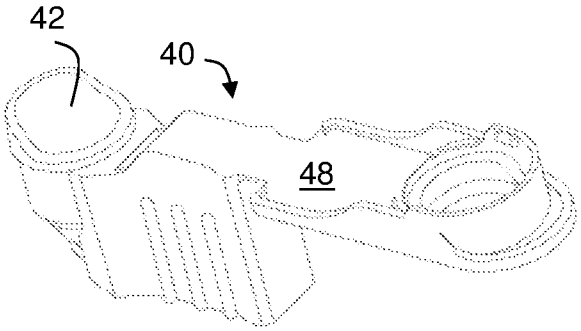


FIG. 3D

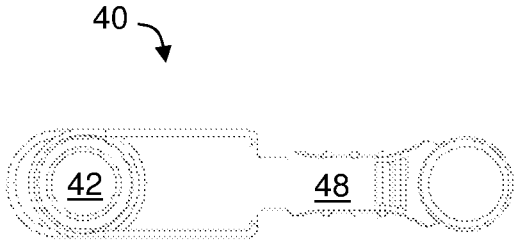


FIG. 3E

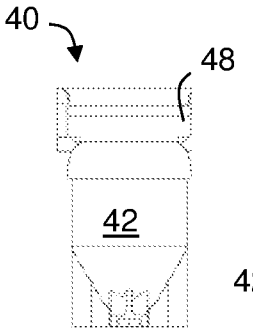


FIG. 3F

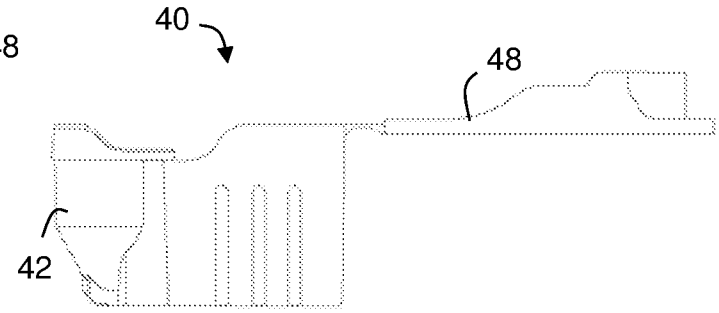
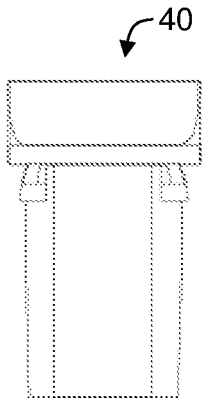


FIG. 3G



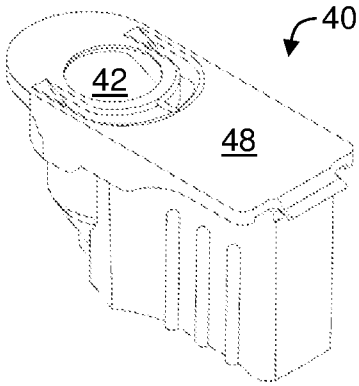


FIG. 3H

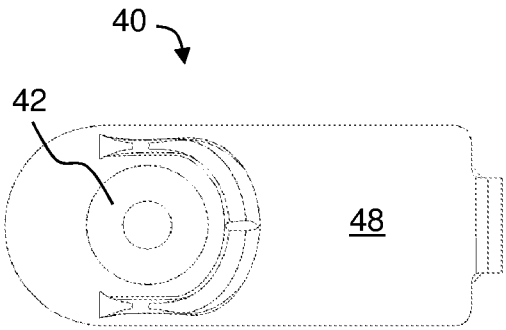


FIG. 3I

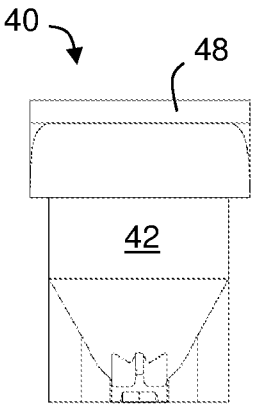


FIG. 3J

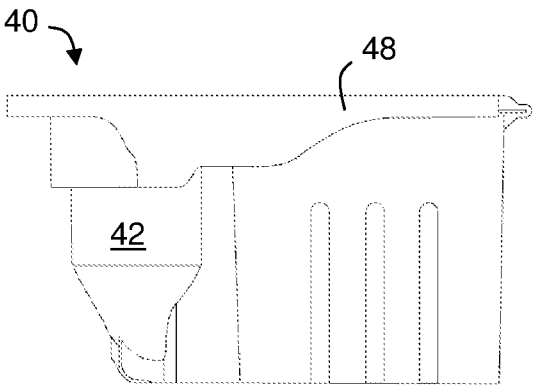


FIG. 3K

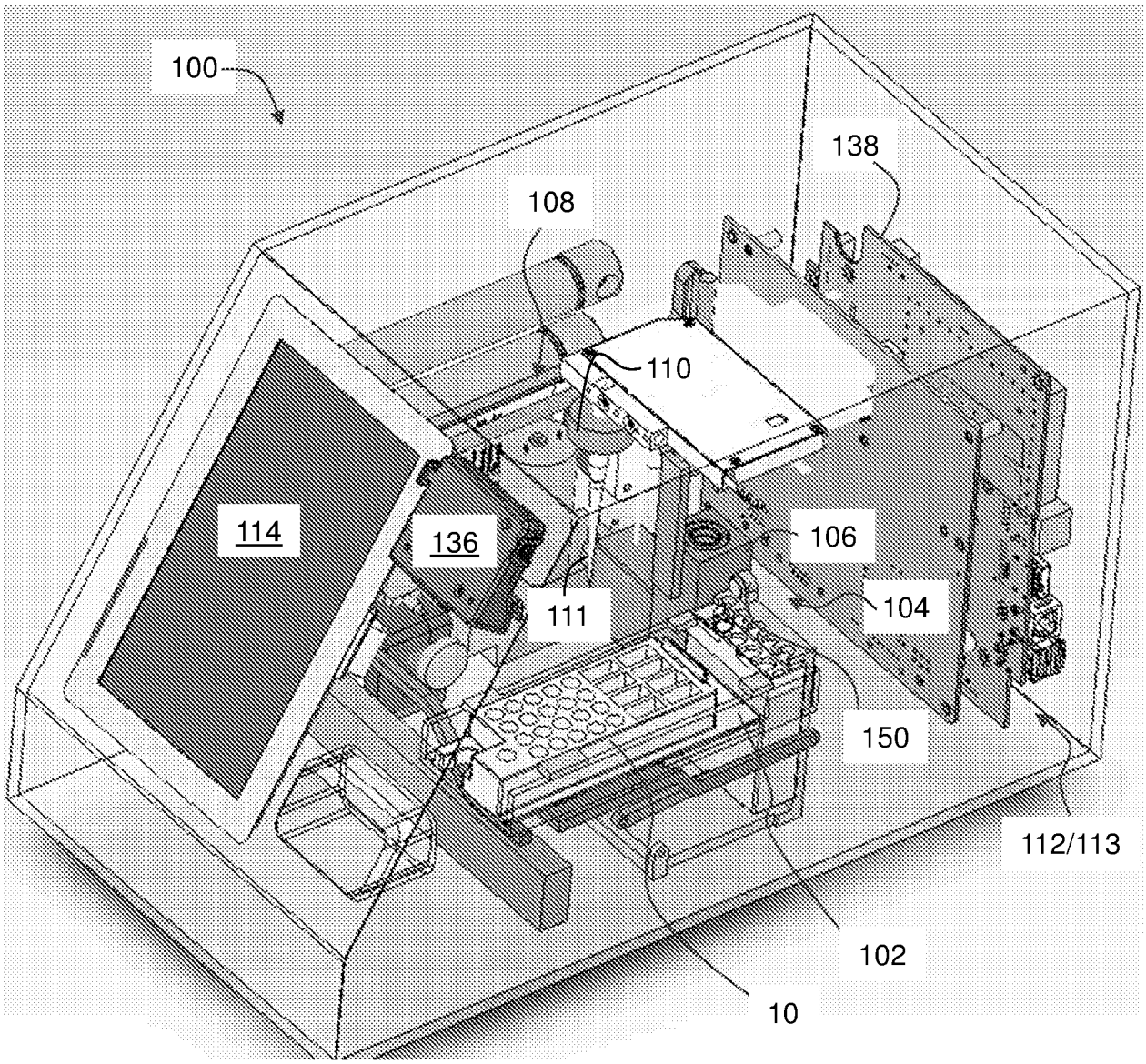


FIG. 4

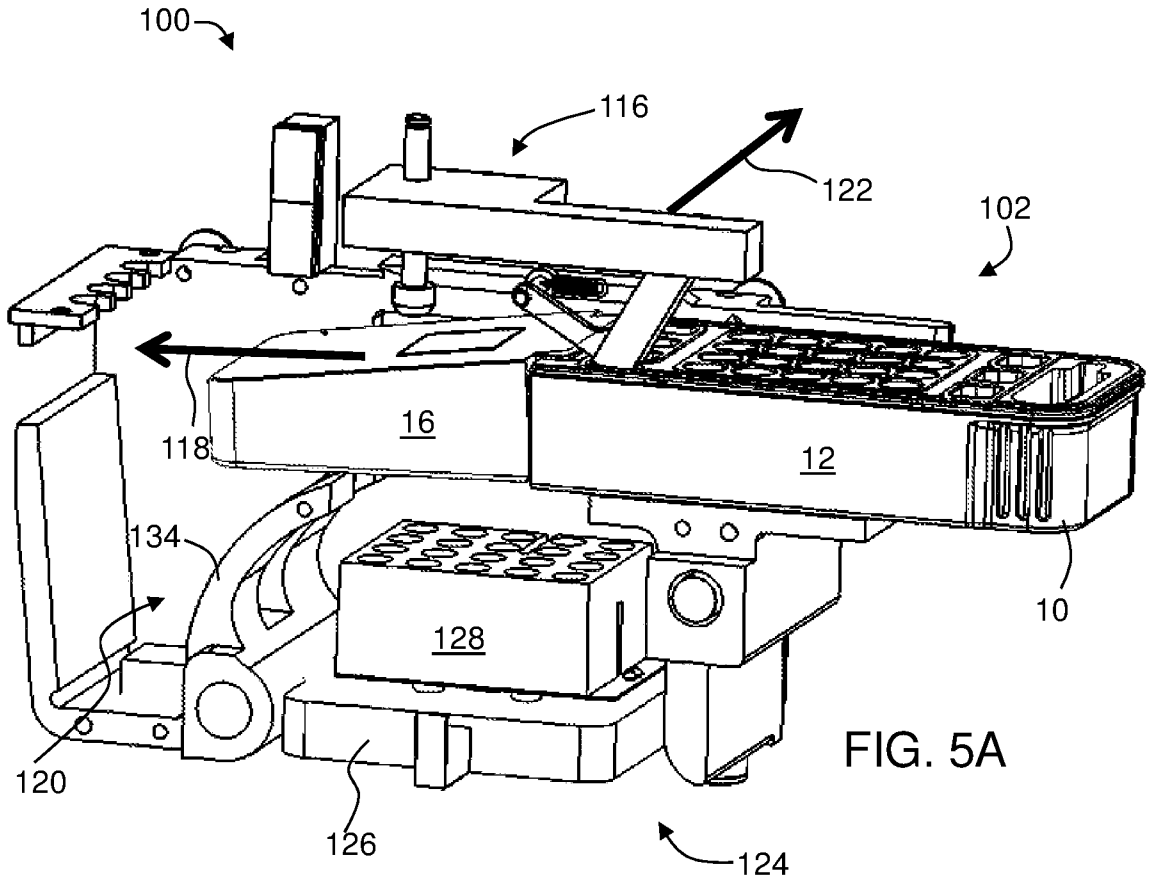

100
116
122
102
16
118
12
134
10
128
120
126
124

FIG. 5A

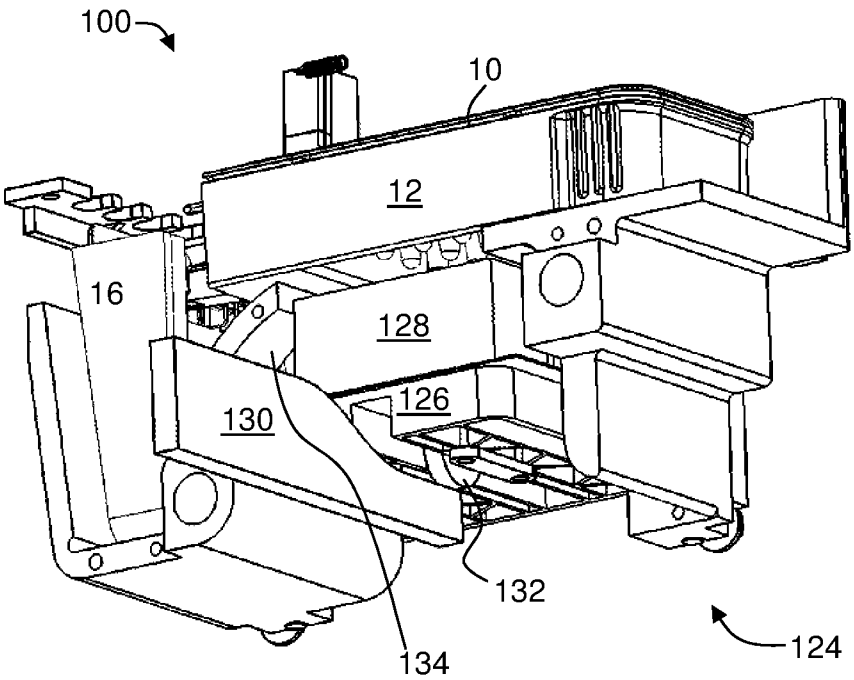

100
10
12
16
128
126
130
132
134
124

FIG. 5B

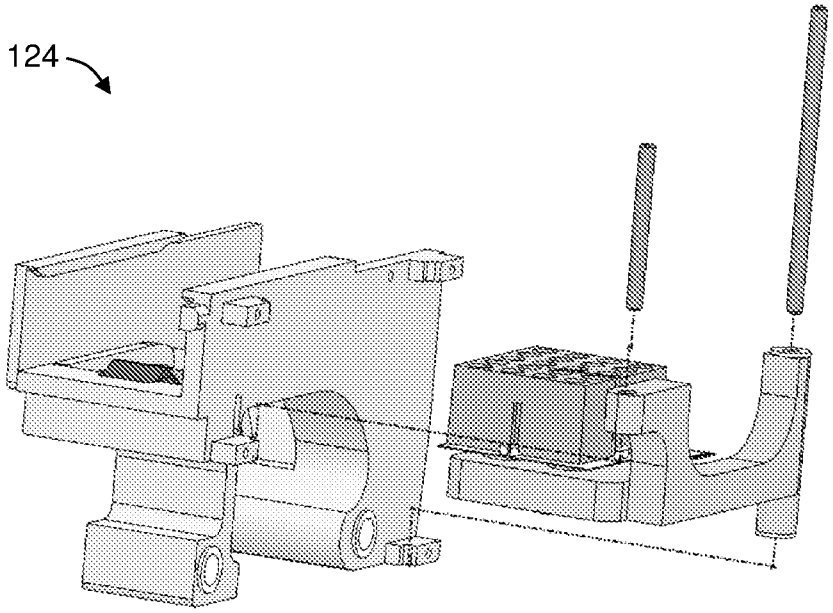


FIG. 5C

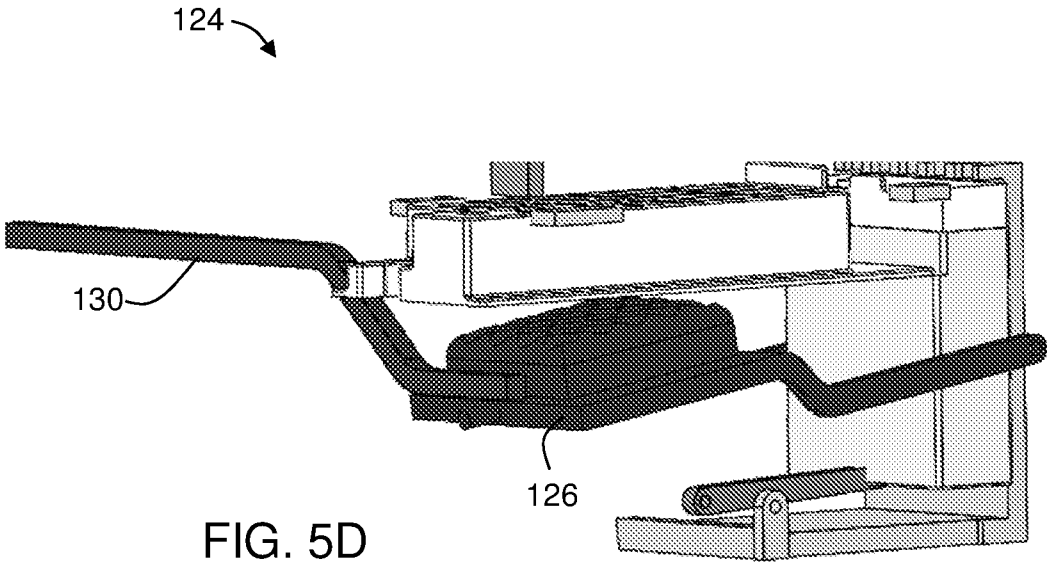


FIG. 5D

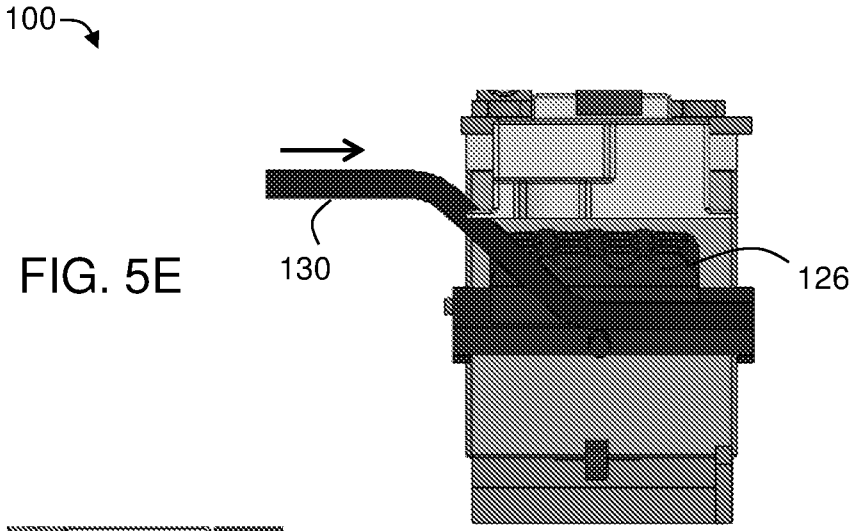


FIG. 5E

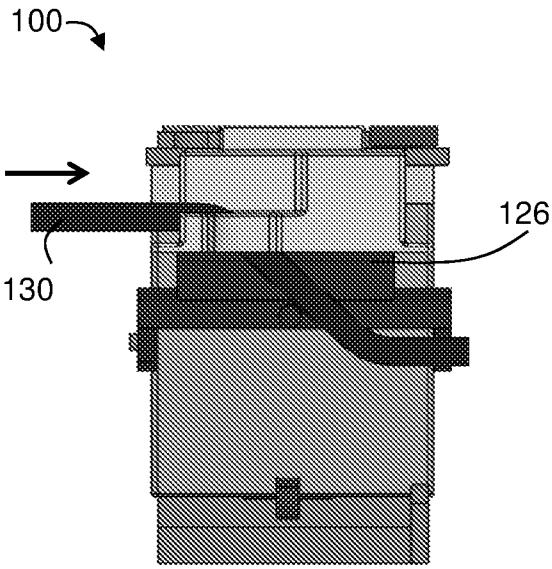


FIG. 5F

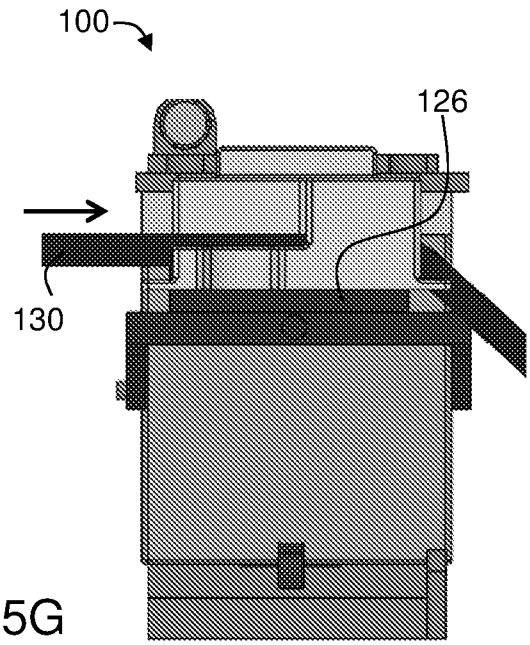


FIG. 5G

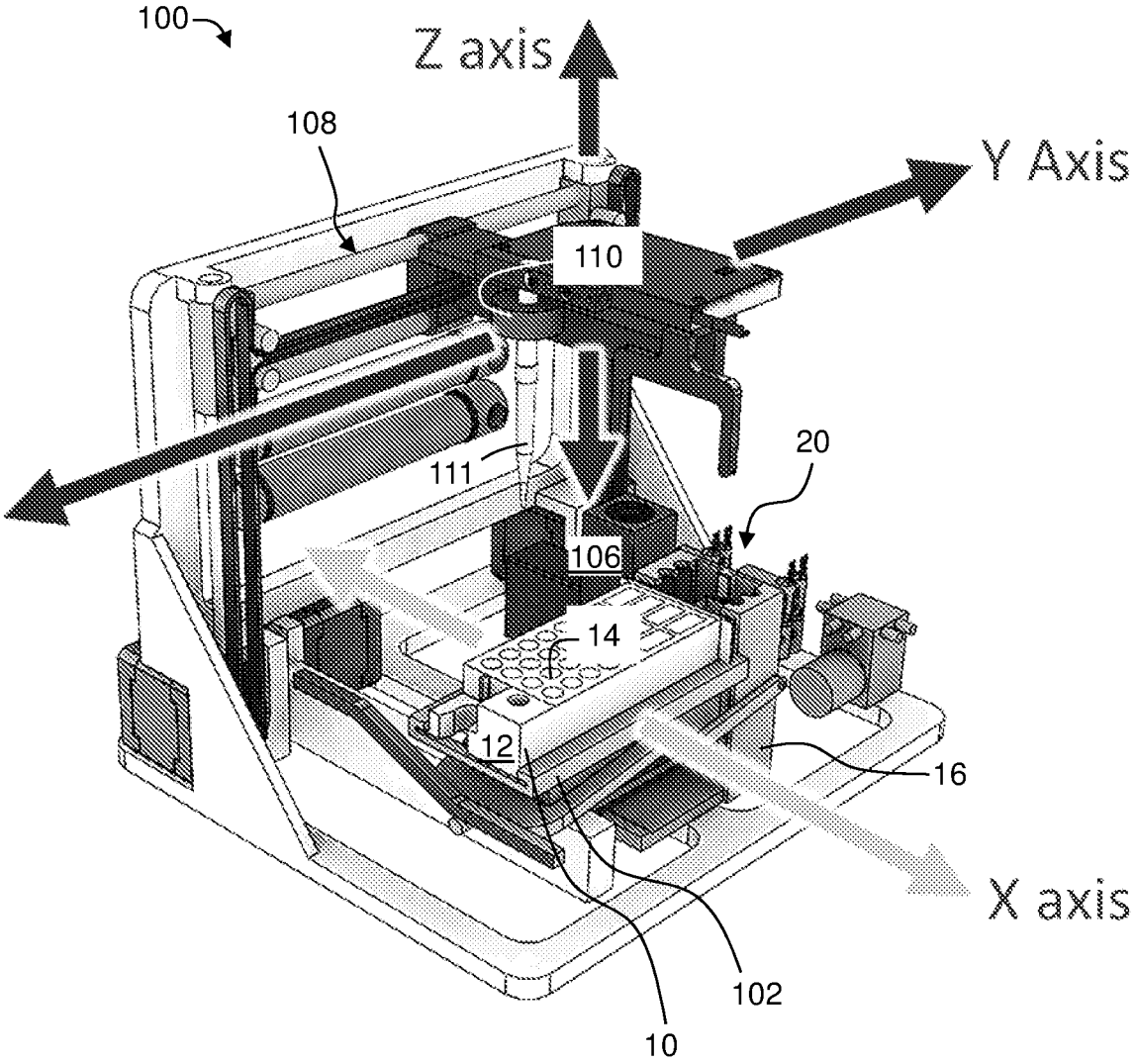


FIG. 6A

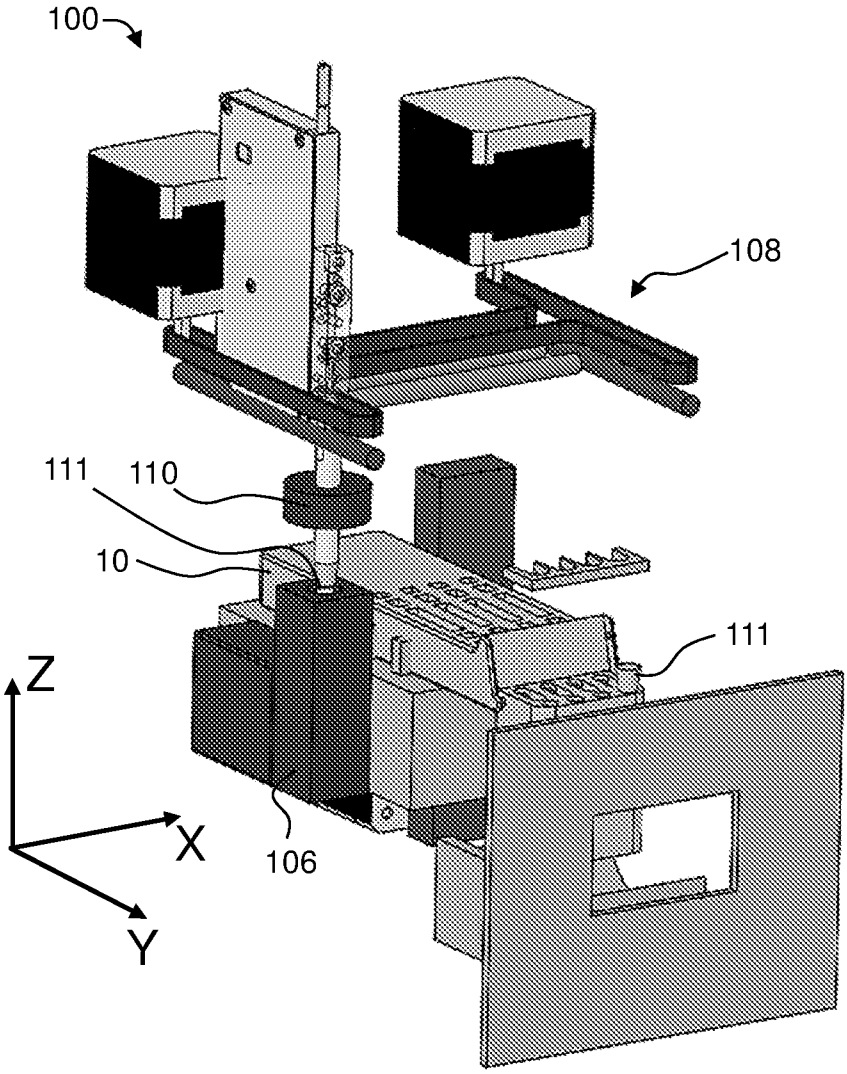


FIG. 6B

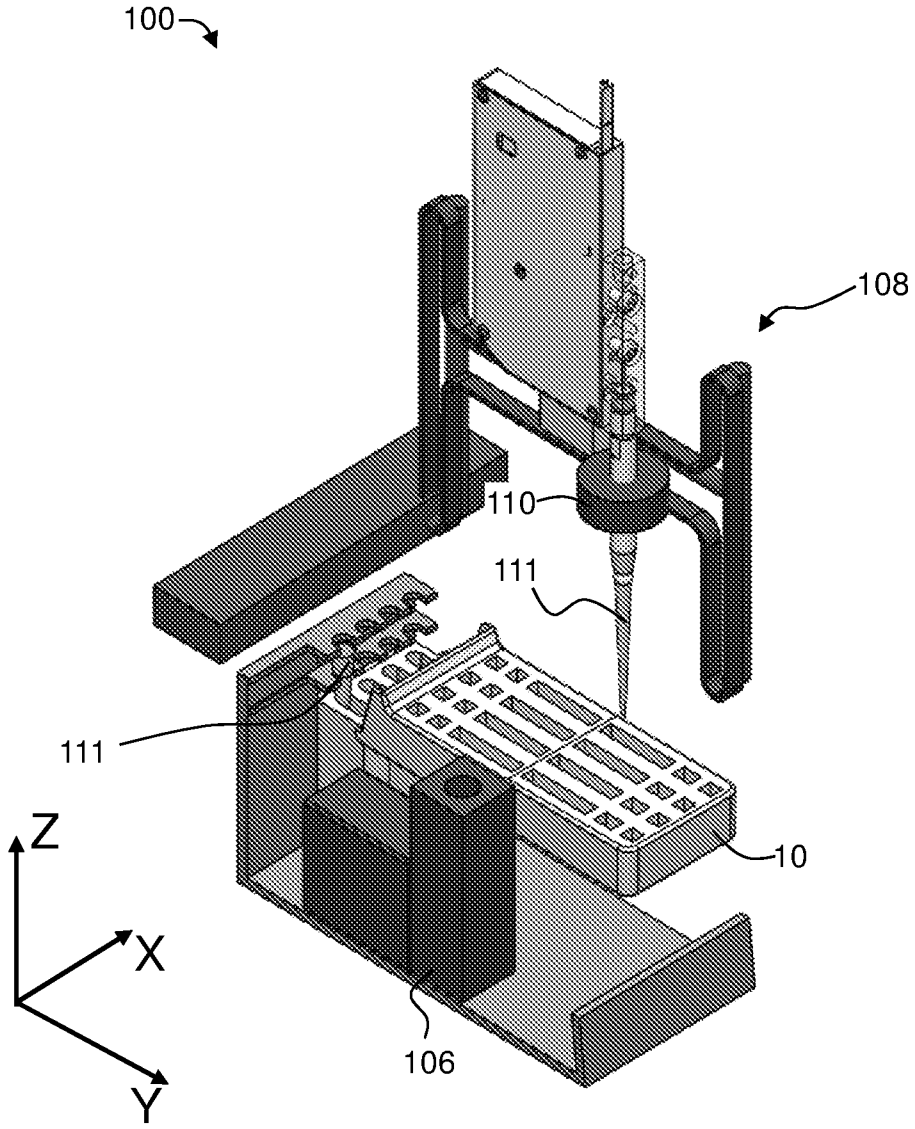


FIG. 6C

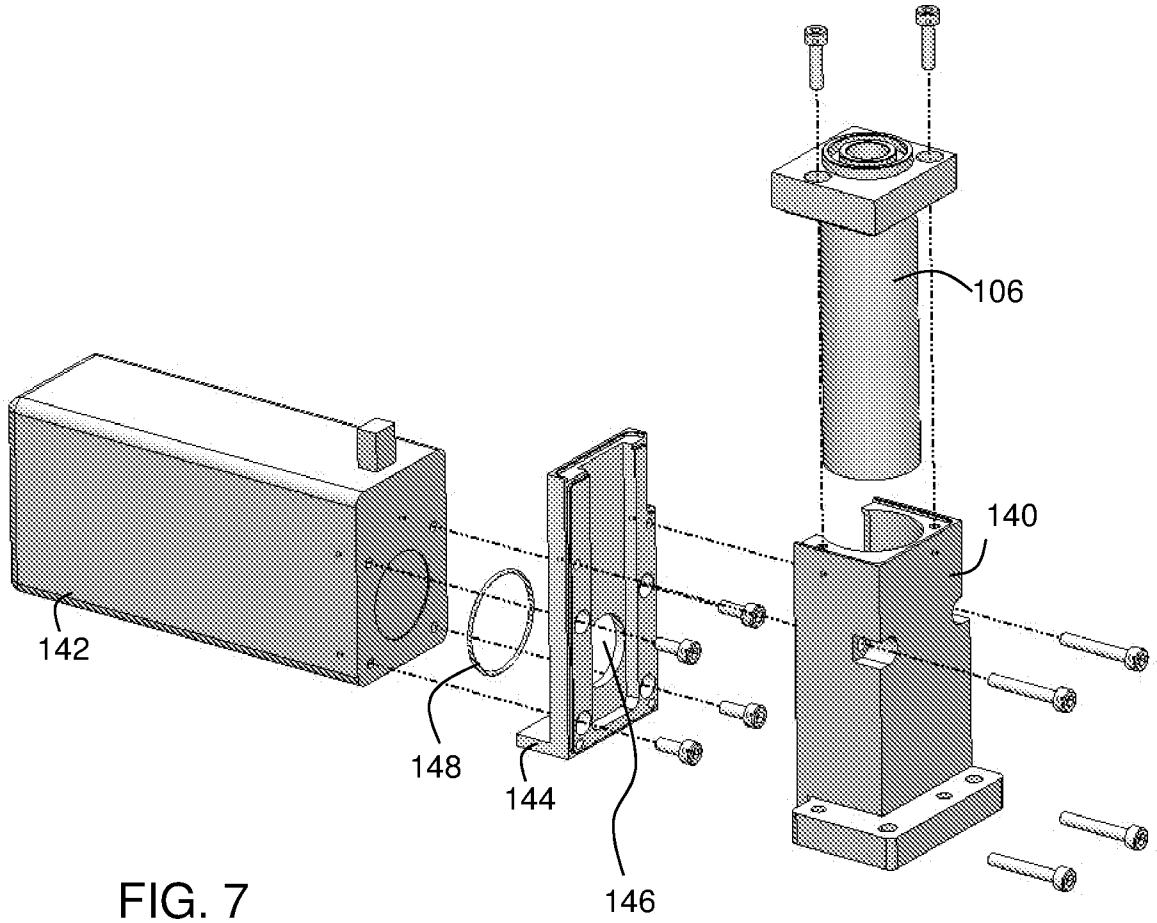


FIG. 7

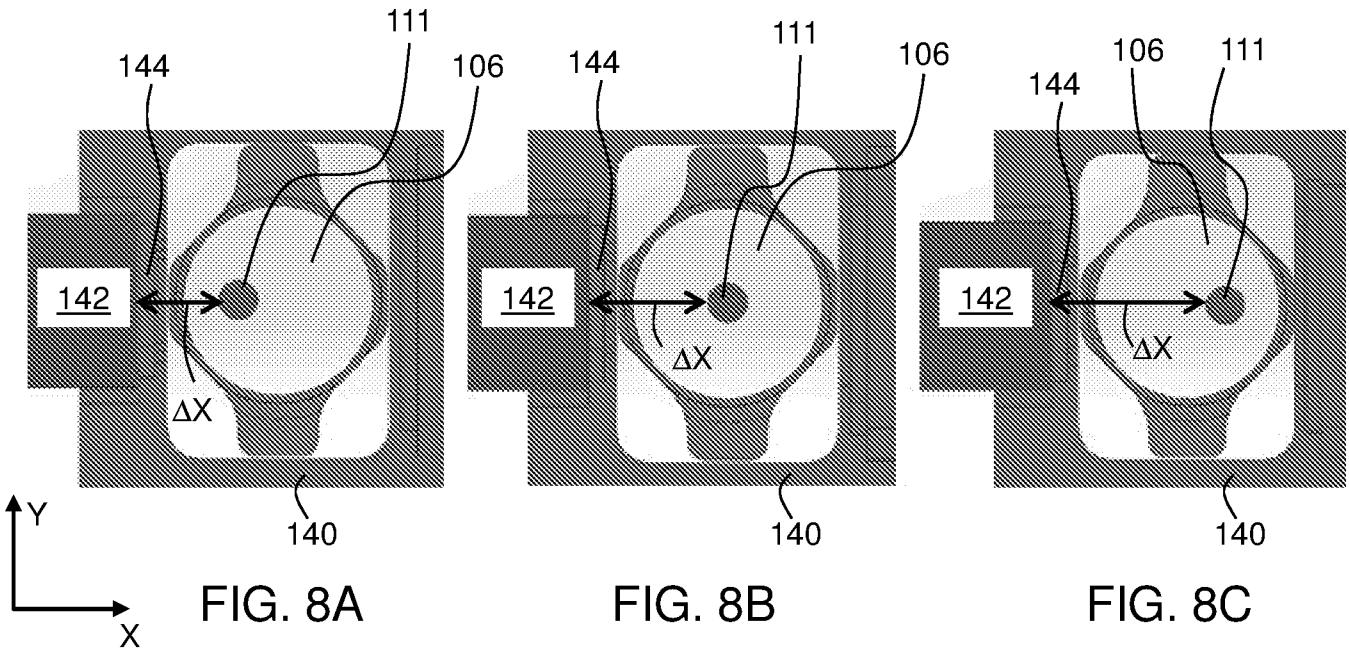


FIG. 8A FIG. 8B FIG. 8C

FIG. 9

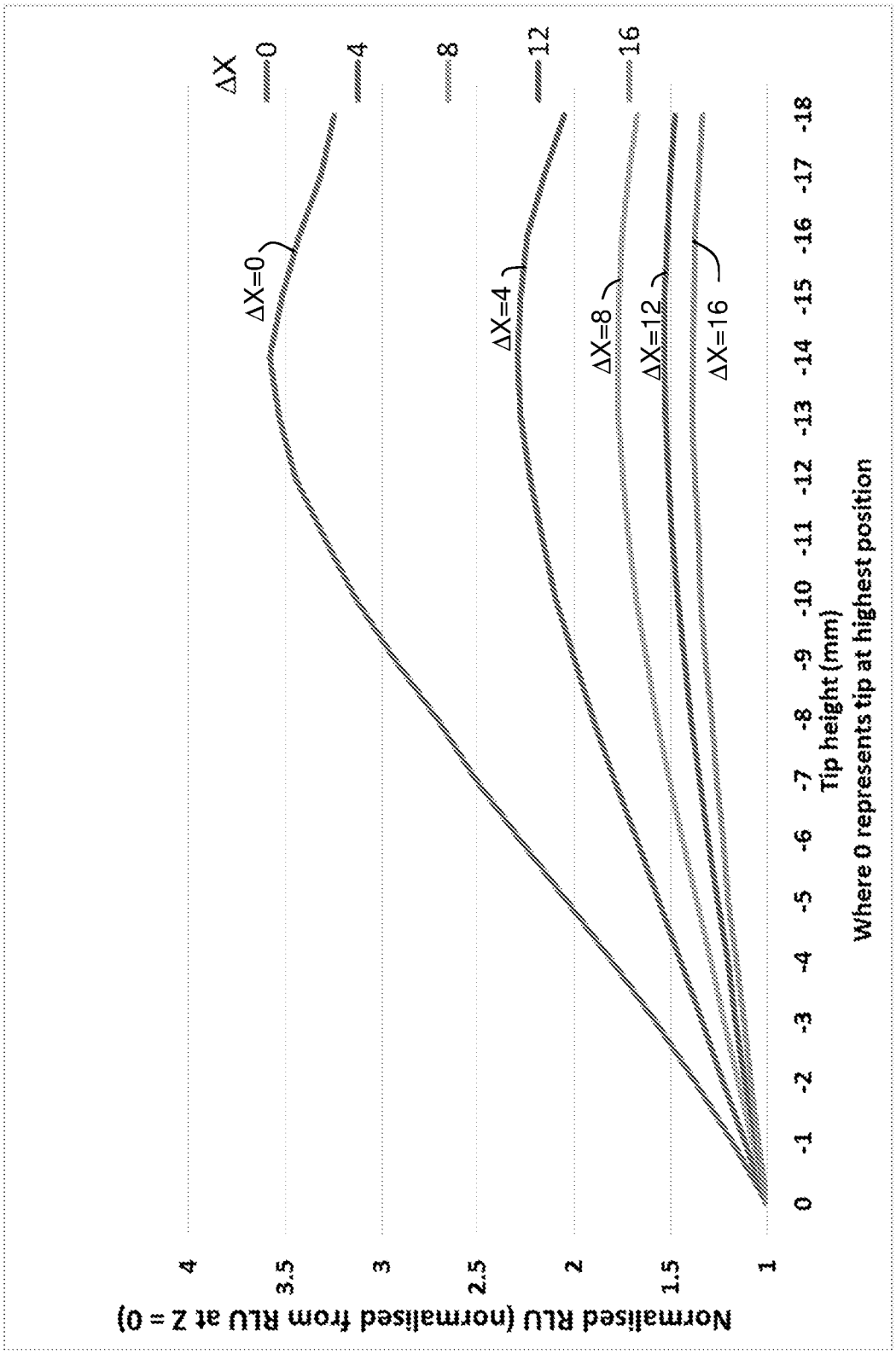
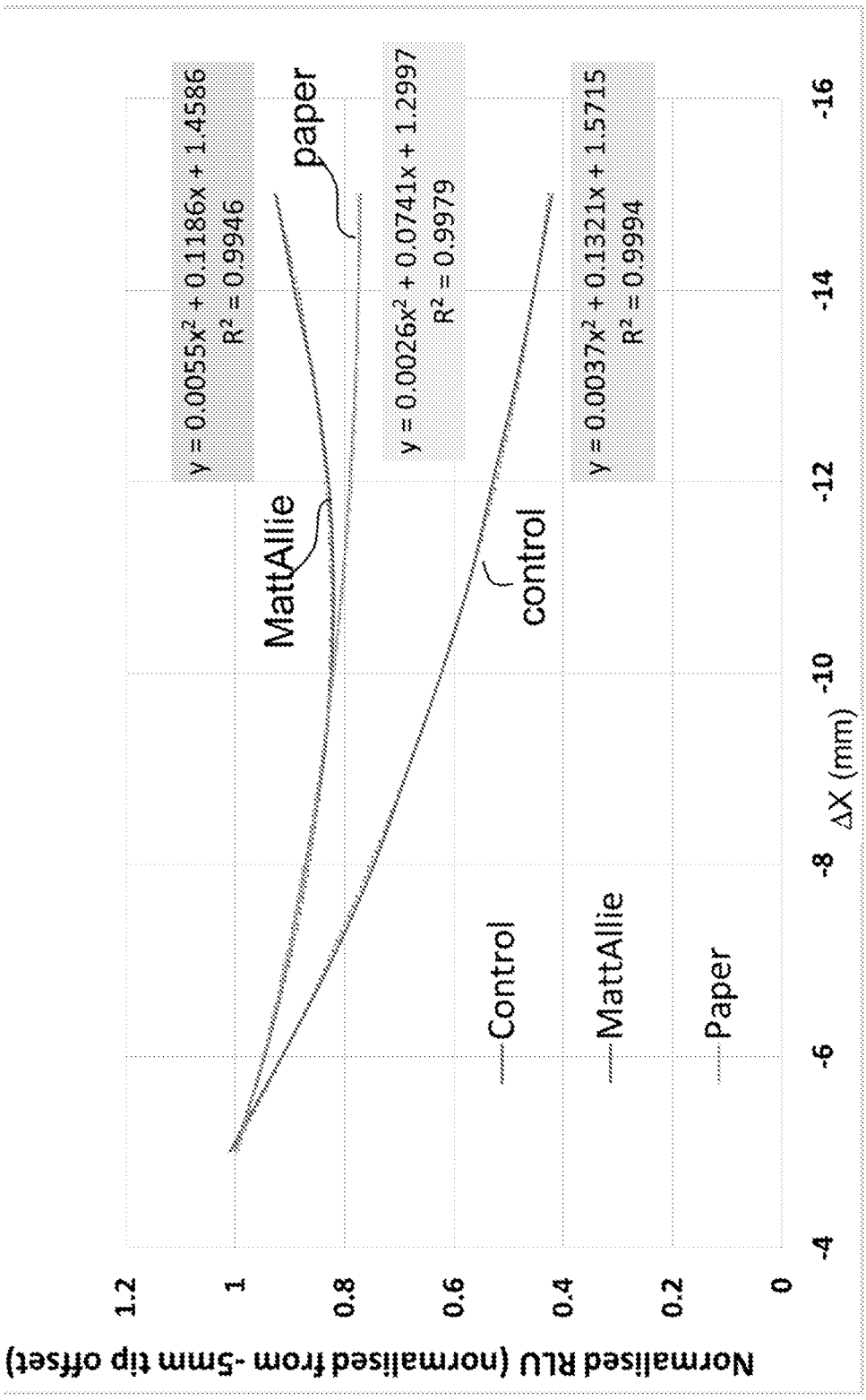

ΔX
0
4
8
12
16
ΔX=0
ΔX=4
ΔX=8
ΔX=12
ΔX=16
Normalised RLU (normalised from RLU at Z = 0)
4
3.5
3
2.5
2
1.5
1
0 -1 -2 -3 -4 -5 -6 -7 -8 -9 -10 -11 -12 -13 -14 -15 -16 -17 -18
Tip height (mm)
Where 0 represents tip at highest position

FIG. 10


Normalised RLU (normalised from -5mm tip offset)
1.2
1
0.8
0.6
0.4
0.2
0
-4
-6
-8
-10
-12
-14
-16
ΔX (mm)
y = 0.0055x² + 0.1186x + 1.4586
R² = 0.9946
y = 0.0026x² + 0.0741x + 1.2997
R² = 0.9979
y = 0.0037x² + 0.1321x + 1.5715
R² = 0.9994
MattAllie
paper
control
Control
MattAllie
Paper

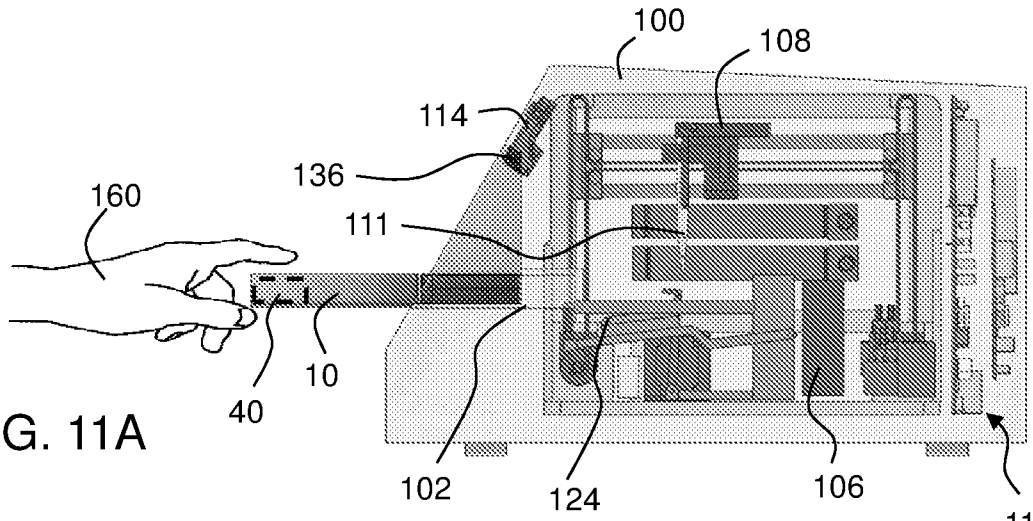


FIG. 11A

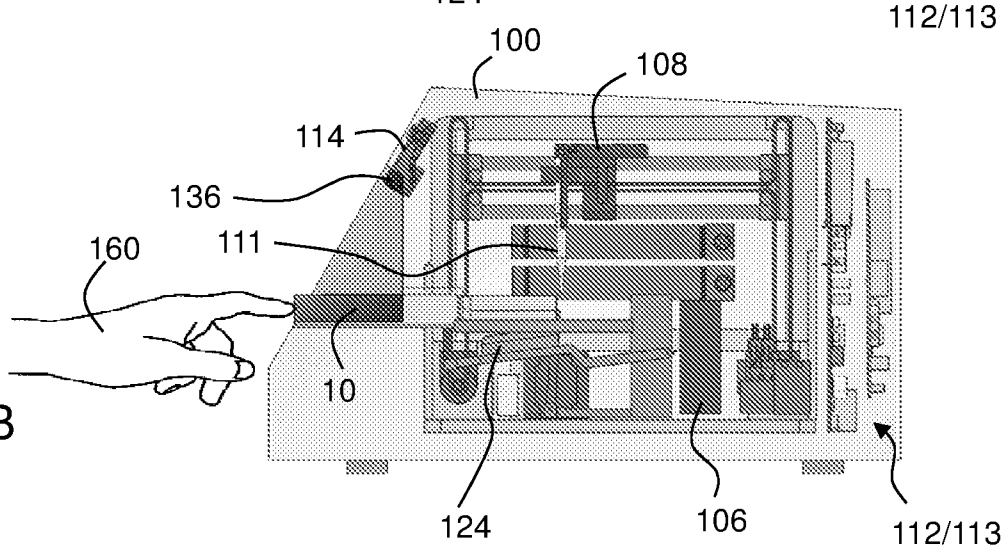


FIG. 11B

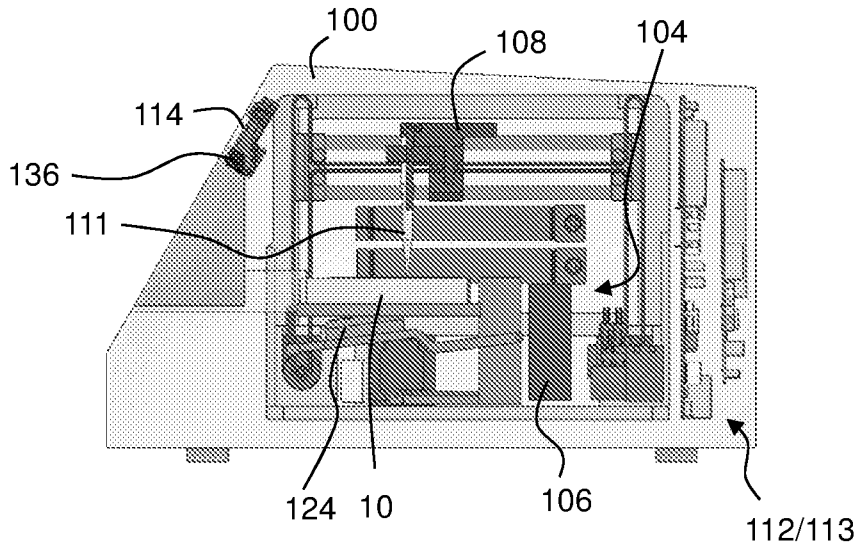
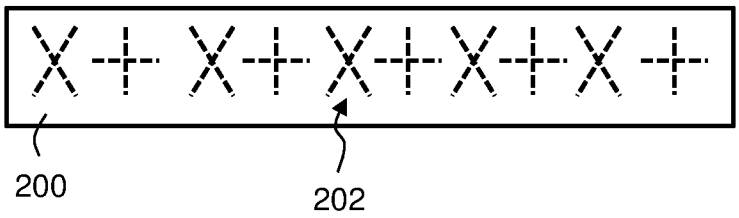


FIG. 11C

FIG. 12



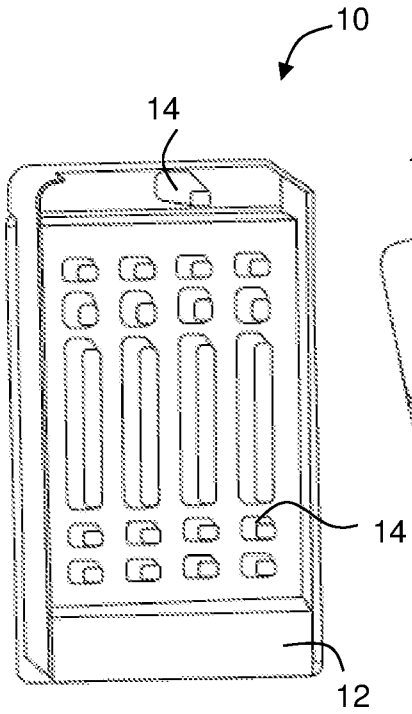


FIG. 13A

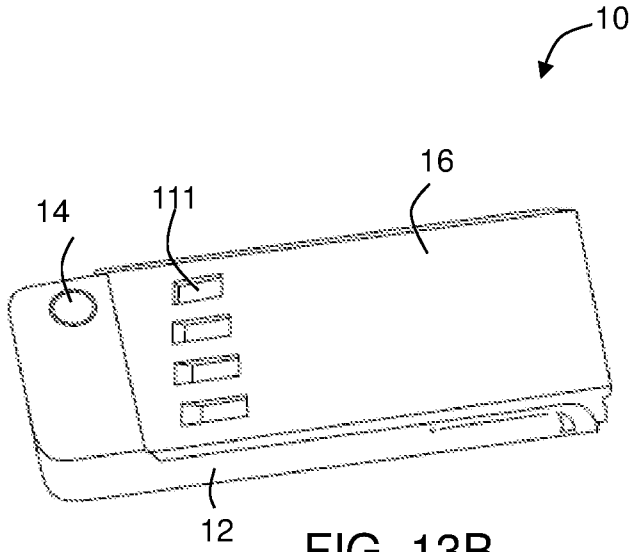


FIG. 13B

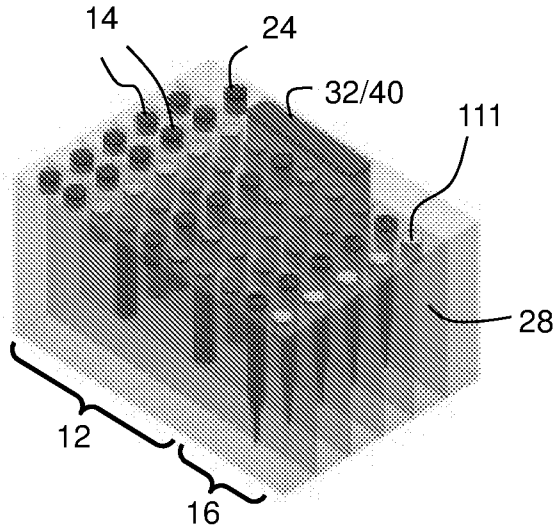


FIG. 14A

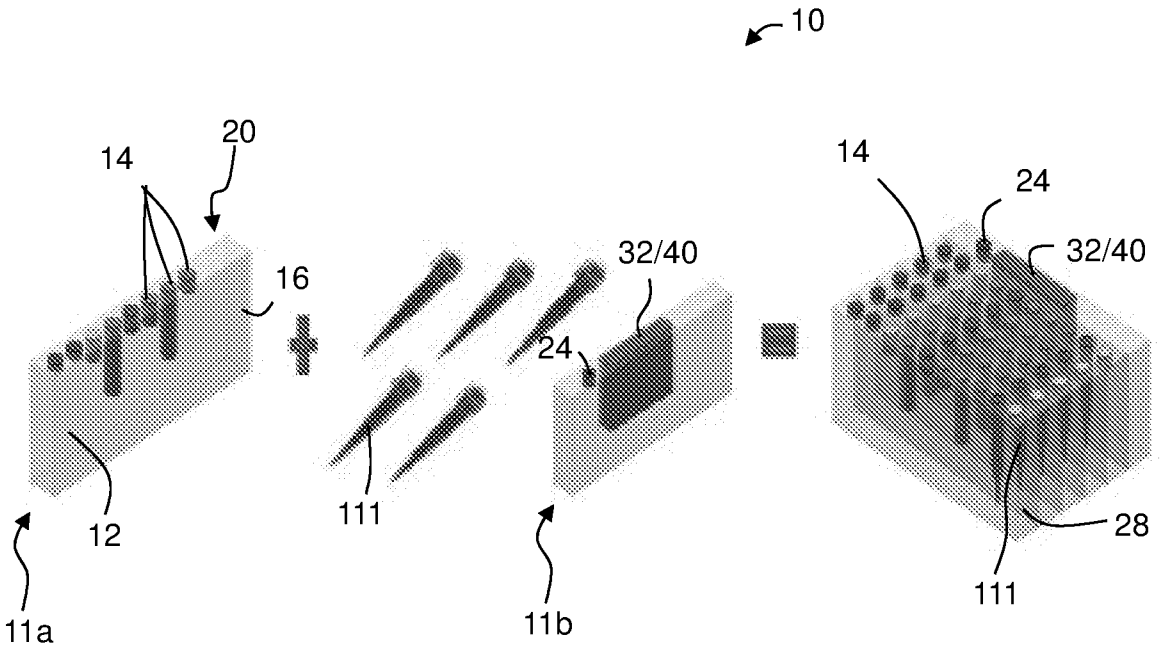


FIG. 14B

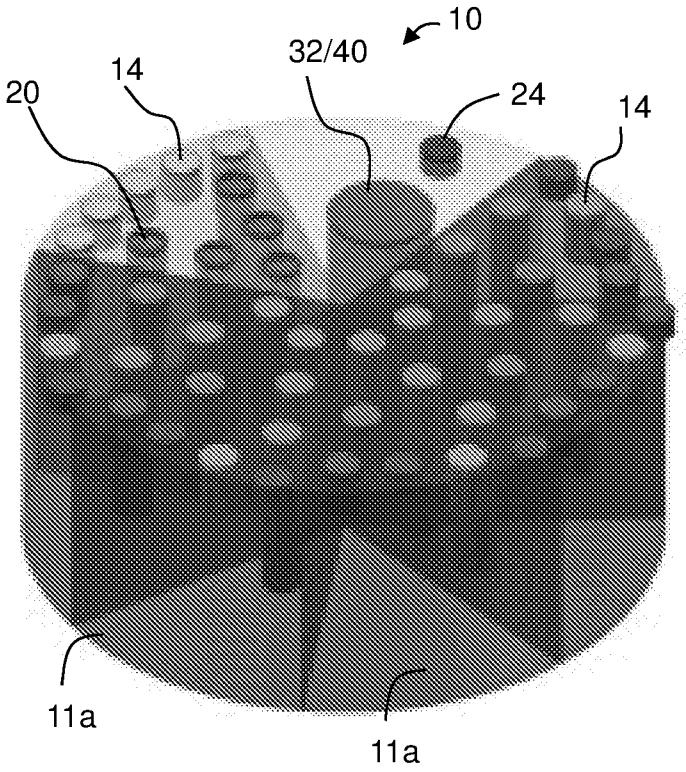


FIG. 15A

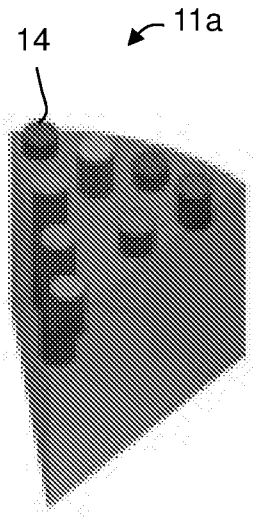


FIG. 15B

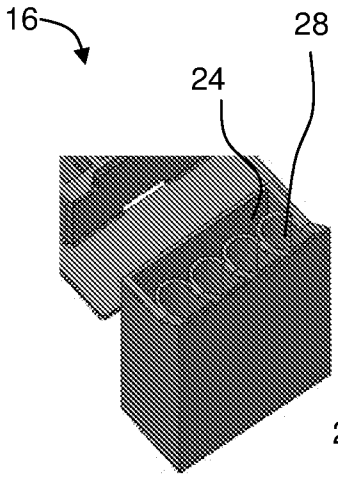


FIG. 16A

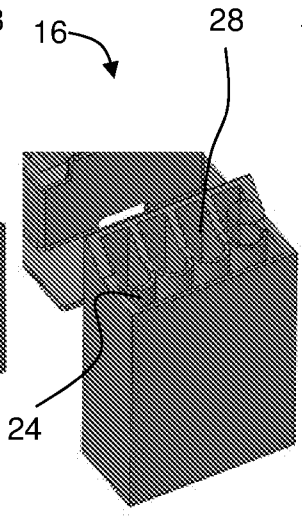


FIG. 16B

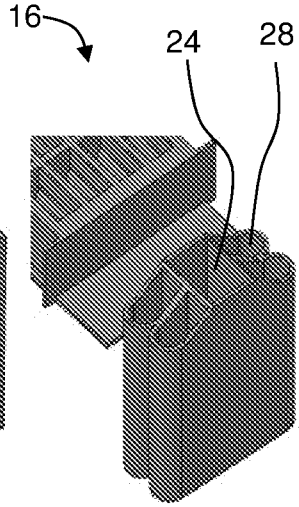


FIG. 16C

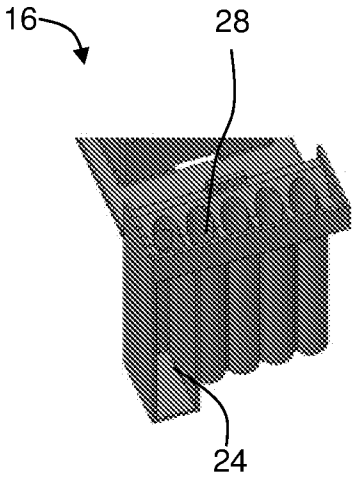


FIG. 16D

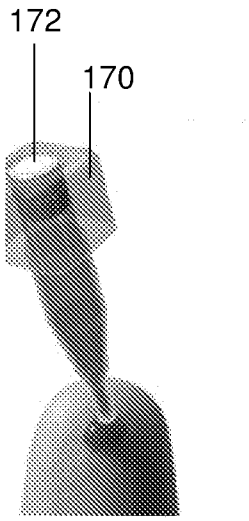


FIG. 17A

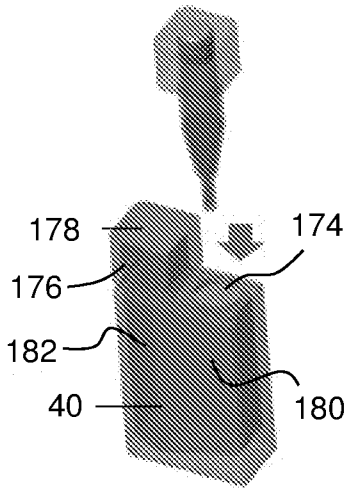


FIG. 17B

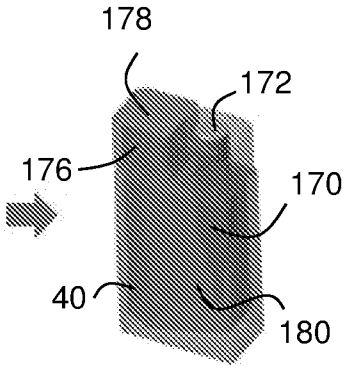


FIG. 17C

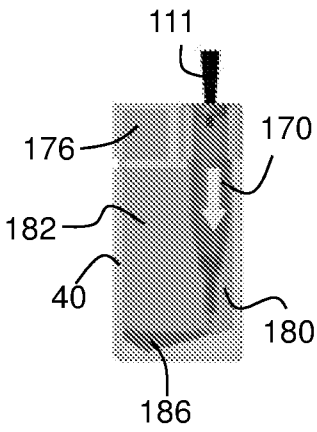


FIG. 17D

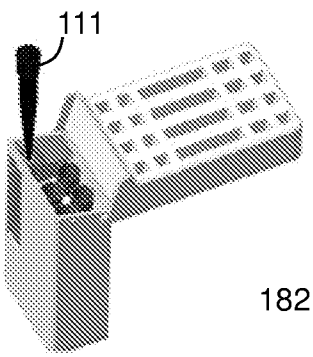


FIG. 17E

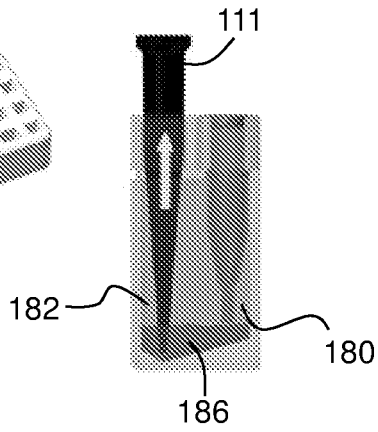


FIG. 17F

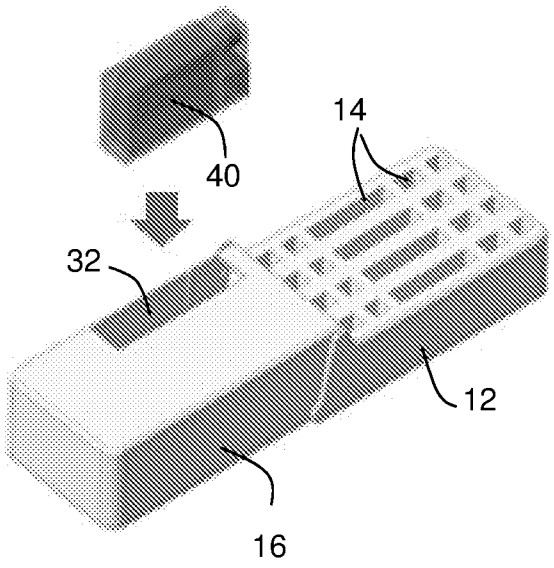


FIG. 18A

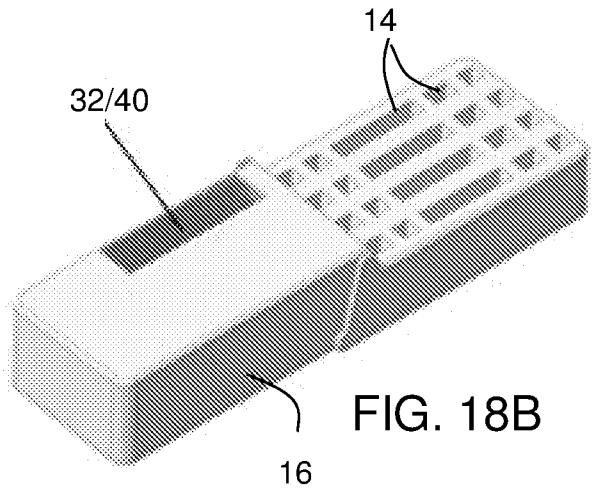


FIG. 18B

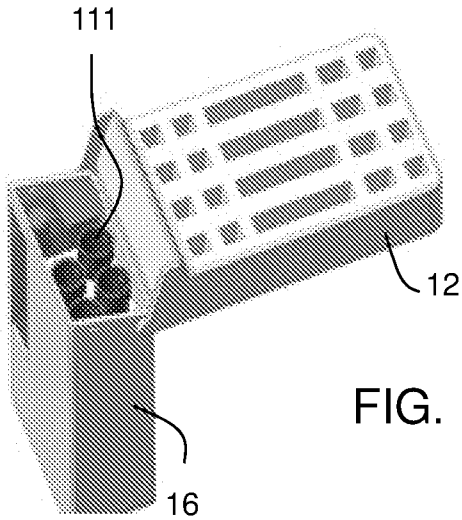


FIG. 18C

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL2018/050972

A. CLASSIFICATION OF SUBJECT MATTER

IPC (2018.01) A61B 5/15, B01L 3/00, B01L 7/00, G01N 1/38, G01N 33/53, G01N 33/569, G01N 35/10, G01N 21/76, A61B 10/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC (2018.01) G01N 33/53

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

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

Databases consulted: Esp@cenet, Google Patents, Derwent Innovation, Orbit
Search terms used: robotic arm, assay, cartridge, optical, analysis, waste, reflect, coat, reaction chamber, detection chamber, analysis chamber, chemiluminescence, modular, poc, point of care, chamber, assay, tip, analysis,

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2009088336 A1 THERANOS, INC et al 02 Apr 2009 (2009/04/02) The whole document	1-41,44-70,73
Y	The whole document	71,72
Y	WO 02090995 A2 AXIS-SHIELD ASA; HOLTLUND, JOSTEIN; BORCH, STIG, MORTEN; SEIM, THORSTEIN; JANSON, TORE; TOEN, HEGE; KARLSON, JAN, ROGER; LAUVSTAD, INGER, LISE; COCKBAIN, JULIAN 14 Nov 2002 (2002/11/14) p. 18, line 15 – p. 19, line 1	71,72
Y	WO 2013043203 A2 THERANOS, INC; HOLMES, ELIZABETH; BALWANI, SUNNY; ROY, JOY; FRANKOVICH, JOHN, KENT; FRENZEL, GARY 28 Mar 2013 (2013/03/28) p. 169, para. [0734]-[0735]; p. 194, para. [0836], lines 7-9 & para. [0839]-[0840]	72
A	WO 0111374 A2 BIOSTAR, INC; THERMO BIOSTAR, INC 15 Feb 2001 (2001/02/15) The whole document	1-41,44-73

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

[X] See patent family annex.

* Special categories of cited documents:

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 Dec 2018	26 Dec 2018

Name and mailing address of the ISA:
Israel Patent Office
Technology Park, Bldg.5, Malcha, Jerusalem, 9695101, Israel
Facsimile No. 972-2-5651616

Authorized officer
ITIN Yulia
YuliaI@justice.gov.il
Telephone No. 972-2-5651680

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL2018/050972

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CN 101098956 B MESO SCALE TECHNOLOGIES LLC 23 May 2012 (2012/05/23) The whole document	1-41,44-73

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL2018/050972

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

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

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

2. ☒ Claims Nos.: 42,43
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
The formulation of these claims is very unclear, so no meaningful search could be carried out.

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

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

This International Searching Authority found multiple inventions in this international application, as follows:
See extra sheet.

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

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

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

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

Remark on Protest

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

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

☐ No protest accompanied the payment of additional search fees.

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

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

Invention/s 1	A cartridge for analyzing a body liquid, comprising a plurality of wells and a compartment for holding at least one disposable pipette tip.	Claim/s 1-5,7-41,44,45,59-62,64-72
Invention/s 2	A kit for analyzing a body liquid, comprising a plurality of wells and a compartment for holding at least one disposable tip.	Claim/s 6,8,10,12,14,16,18,20,22,24,26,28,30,32,35,37,41,45,60,62,64-72
Invention/s 3	A cartridge for analyzing a body liquid, comprising a first plurality of wells with a tapered base and a second plurality of wells with a non-apered base, formed in a monolithic structure.	Claim/s 46-58
Invention/s 4	A system for analyzing a body liquid, comprising a first and second cartridge holders, an internal analyzer system, a robotic arm and a controller.	Claim/s 63-72
Invention/s 5	A method for analyzing a body liquid comprising providing a pipette tip containing the body liquid, and an antibody conjugated to an enzyme and a substrate generating chemiluminescence signal during reaction of said body liquid with said antibody within said tip, and operating an optical analyzer to detect said chemiluminescent signal from said pipette tip.	Claim/s 73

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IL2018/050972

Patent document cited search report	Publication date	Patent family member(s)	Publication Date
US 2009088336 A1	02 Apr 2009	US 2009088336 A1	02 Apr 2009
		US 8088593 B2	03 Jan 2012
		AU 2008308686 A1	09 Apr 2009
		AU 2008308686 B2	22 Jan 2015
		AU 2011310111 A1	04 Apr 2013
		AU 2011310111 B2	14 Aug 2014
		AU 2011310111 C1	07 May 2015
		AU 2011310111 B9	24 Nov 2016
		AU 2011310111 C9	24 Nov 2016
		AU 2013205047 A1	16 May 2013
		AU 2013205047 A8	30 May 2013
		AU 2013205047 B2	22 Jan 2015
		AU 2013205052 A1	16 May 2013
		AU 2013205052 A8	13 Jun 2013
		AU 2013205052 B2	16 Apr 2015
		AU 2015201617 A1	16 Apr 2015
		AU 2017235899 A1	12 Oct 2017
		BR PI0820328 A2	16 Aug 2016
		CA 2701794 A1	16 Apr 2009
		CA 2701794 C	31 Oct 2017
		CA 2812901 A1	05 Apr 2012
		CA 2934220 A1	16 Apr 2009
		CL 2013000865 A1	28 Mar 2014
		CN 101874205 A	27 Oct 2010
		CN 101874205 B	01 Oct 2014
		CN 103118664 A	22 May 2013
		CN 103118664 B	25 Nov 2015
		CN 103323610 A	25 Sep 2013
		CN 103323610 B	28 Dec 2016
		CN 104297506 A	21 Jan 2015
		CN 104297506 B	03 May 2017

INTERNATIONAL SEARCH REPORT
Information on patent family members

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