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(71) Applicant *(for all designated States except US)*: **MEDTRONIC, INC.** [US/US]; 710 Medtronic Parkway MS LC340, Minneapolis, Minnesota 55432 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **HINIDUMA-LOKUGE, Prasanga, D.** [US/US]; 215 Oak Street, Number 806, Minneapolis, Minnesota 55403 (US). **SIGG, Daniel, C.** [US/US]; 1485 Hoyt Avenue West, St. Paul, Minnesota 55108 (US).

(74) Agents: **BARRY, Carol, F.** et al.; 710 Medtronic Parkway MS LC340, Minneapolis, Minnesota 55432 (US).

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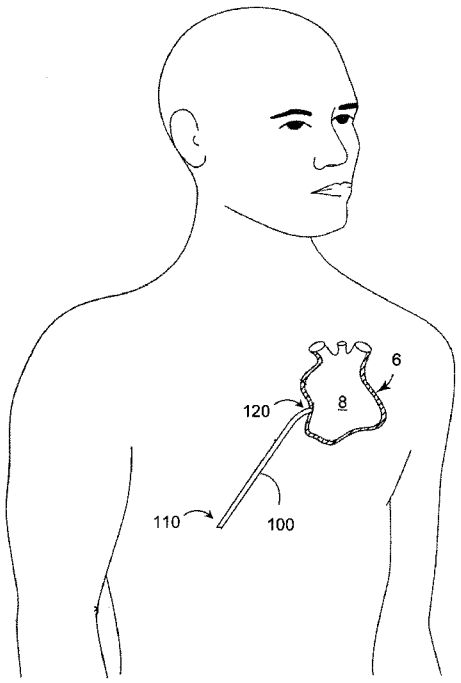

FIG. 1

(57) Abstract: A container (200) for housing a therapeutic agent includes a body member (210), a sealing (220) element, and a rupturable membrane (250). The body member has a proximal end and a distal end and a lumen that extends from the proximal end to the distal end. The sealing element is slidably disposable in the lumen. The sealing element is configured to sealingly engage the body member as the element is slid within the lumen. The rupturable membrane is disposed across the lumen in proximity to the distal end of the body member.

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SYSTEM AND METHOD FOR DELIVERY OF BIOLOGIC AGENTS

FIELD

This disclosure relates to medical devices, systems and methods for delivering biologic agents to a patient.

BACKGROUND

Systems for delivering biologic agents in an operating room setting currently include the biologic agent and a delivery device. A mapping/navigation system, and a monitor for viewing the delivery process may also be used. The biologic agent is typically delivered to the operating room in an appropriate volume and concentration in a closed container, such as an Eppendorf tube. Once in the operating room and when the delivery device is ready to receive this biologic agent, the biologic agent is transferred from the container to a syringe which is in turn connected to the delivery device. The biologic agent is then carefully delivered from the syringe through the delivery device into target tissue.

The steps involved in such a process present several areas for improvement. For example, the transfer of the biologic agent from the container to the delivery system involves exposing the agent to the environment, risking contamination. Also, the transfer provides the potential for spilling and loss of the biologic agent, as well as potentially inaccurate amounts being delivered. Further, the number of different materials that the biologic agent contacts may be quite high. For example, the biologic agent contacts the container, such as the Eppendorf tube, the syringe, and the delivery device, allowing for possible compatibility issues and losses due to adhesion and adsorption to the container, syringe and delivery device.

Another source of potential concern with current methods for delivering biologic agents is excessive shear stress being placed on the biologic agent as it is delivered through the delivery system. The delivery system typically includes catheters having very small inner diameters; e.g., 29-27G or about 0.007 inches to 0.009 inches. The inner diameters of the catheters are purposefully kept small to reduce dead space and thus to

minimize the amount of deliverable biologic agent lost during the procedure. Exposure to shear stress may greatly reduce the efficacy of the biologic agent delivered, particularly cells.

BRIEF SUMMARY

This disclosure describes, inter alia, a system for delivering biologic agents that allows for delivery of biologic agents in a container via a catheter to a target tissue of a patient. As disclosed herein, an appropriate or predetermined amount of biologic agent may be transferred into the container in a sterile environment. In the operating room, the container is placed in a catheter having a distal end implanted at a target tissue site of a patient and is moved to the distal end of the catheter, where its contents are released into the target tissue. For purposes of brevity and clarity, containers are described herein in the context of biologic delivery systems. However, it will be understood that the containers may have utility outside of such systems; e.g., for general storage and housing.

In an embodiment, a container for housing a therapeutic agent is described. The container includes a body member, a sealing element, and a rupturable membrane. The body member has a proximal end and a distal end and a lumen that extends from the proximal end to the distal end. The sealing element is slidably disposable in the lumen. The sealing element is configured to sealingly engage the body member as the element is slid within the lumen. The rupturable membrane is disposed across the lumen in proximity to the distal end of the body member.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG.1 is a schematic view of a partially implanted catheter in the environment of a patient.

FIG. 2 is a schematic perspective view of a representative delivery system.

FIG. 3 is a schematic side view of a catheter and tube with complementary connector fittings.

FIGs. 4A-D are schematic longitudinal cross sections of representative catheters.

FIGs. 5A-B and **6A-B** are schematic longitudinal cross sections of representative containers.

FIGs. 7-11 are schematic longitudinal cross sections of representative delivery systems.

FIG. 12-14 are block diagrams of representative components of control and drive systems of representative delivery systems

FIG. 15 is a schematic longitudinal cross section of a representative container.

FIGs. 16 and **17A** are schematic side views of representative two-part containers.

FIG. 17B is a schematic longitudinal cross section of the container depicted in **FIG. 17A**.

FIGs. 18-19 are schematic longitudinal cross sections of representative containers.

FIG. 20 is a block diagram of a container having two chambers.

FIGs. 21-22 are schematic longitudinal cross sections of representative multi-part containers capable of forming two chambers.

The drawings are not necessarily to scale. Like numbers used in the figures refer to like components, steps and the like. However, it will be understood that the use of a number to refer to a component in a given figure is not intended to limit the component in another figure labeled with the same number. In addition, the use of different numbers to refer to components is not intended to indicate that the different numbered components cannot be the same or similar.

DETAILED DESCRIPTION

In the following detailed description, reference is made to the accompanying drawings that form a part hereof, and in which are shown by way of illustration several specific embodiments of devices, systems and methods. It is to be understood that other embodiments are contemplated and may be made without departing from the scope or spirit of the present disclosure. The following detailed description, therefore, is not to be taken in a limiting sense.

All scientific and technical terms used herein have meanings commonly used in the art unless otherwise specified. The definitions provided herein are to facilitate understanding of certain terms used frequently herein and are not meant to limit the scope of the present disclosure.

As used in this specification and the appended claims, the singular forms "a", "an", and "the" encompass embodiments having plural referents, unless the content clearly

dictates otherwise. As used in this specification and the appended claims, the term "or" is generally employed in its sense including "and/or" unless the content clearly dictates otherwise.

As used herein, "have", "having", "include", "including", "comprise", "comprising" or the like are used in their open ended sense, and generally mean "including, but not limited to".

As used herein, the terms "treat", "therapy", and the like mean alleviating, slowing the progression, preventing, attenuating, or curing the treated disease.

As used herein, "disease", "disorder", "condition" and the like, as they relate to a subject's health, are used interchangeably and have meanings ascribed to each and all of such terms.

The present disclosure describes, *inter alia*, systems, devices and methods for delivering biologic agents to a target tissue of a patient. A container housing a therapeutic agent may be placed directly into a delivery system and delivered to the target tissue site where the therapeutic agent may be released. The therapeutic agent may be a biologic agent, such as a cell, a virus, a polypeptide, a polynucleotide or the like. Many of such biologic agents are susceptible to complications due to shear stress due to their large size or molecular weight. The therapeutic agent may be formulated in a solution, suspension, dispersion, or the like or may be in solid form.

Referring now to **FIG. 1**, a catheter **100** of a representative delivery system is schematically shown in the environment of a patient. The catheter **100** has a proximal end **110** and a distal end **120**. In the depicted embodiment, the proximal end **110** of the catheter **100** exterior to the patient, and the distal end **120** is implanted in the patient at a target tissue location, in this case in the pericardial sac **6** of the heart **8**. Biologic agents that are administered intravenously have a relatively short time for contacting cardiac tissue compared to agents delivered into the pericardium. Of course, in various embodiments, it may be desirable to deliver the agent intramyocardially, intracoronary or into the heart in any other suitable manner. While the catheter **100** in **FIG. 1** is depicted as being implanted for delivery of an agent to the heart **8**, it is contemplated that the delivery systems and methods described herein may be used to deliver agent to any suitable target tissue of a patient, including any suitable subcutaneous tissue, including

brain parenchyma, spinal canal, perispinal tissue, cerebrospinal fluid, spleen, pancreas, stomach, intestine, kidney, liver, muscle, and the like.

Referring now to **FIGs. 2-3**, a schematic illustration of some representative components of a delivery system **1000** is shown. The depicted delivery system **1000** includes a catheter **100**, a capsule or container **200** for housing a biologic agent, and a bar **300**. The catheter **100** has a proximal end **110** and a distal end **120** and a body member defining a lumen that extends from the proximal end **110** to the distal end **120** of the catheter **100**. The container **200** is configured to house a biologic agent and is insertable into the lumen of the catheter **100** and slidably disposable in the lumen. The bar **300** is also slidably disposable in the lumen of the catheter **100**, as will be described in more detail below. In the embodiment depicted in **FIG. 2**, a pushing member **350** is coupled to the distal end **320** of the bar **300**. The pushing member **350** may be integrally formed with, connected, attached, bonded, or otherwise coupled to the bar **300**.

As shown in **FIG. 2**, an opening **130** is formed in the body of the catheter **100**. The opening **130** forms a bore in the catheter **100**. The bore intersects the lumen of the catheter **100** and is substantially perpendicular to the axis of the lumen. The opening **130** is configured to receive the container **200** such that the container **200** may be placed in the opening **130** to gain access to the catheter lumen. A cover (not shown) or other member may sealingly engage the opening **130**. The cover or other member may be removed or opened to insert the container **200** into the opening **130**, and replaced to sealingly engage the opening **130** after the container **200** is inserted in the opening. It will be understood, that when catheter **100** does not include such an opening **130** for receiving the container **200**, the container **200** may be inserted into the catheter lumen via an opening at the proximal end **110** of the catheter, through which the lumen extends.

As shown in **FIG. 3**, the proximal end **110** of the catheter **100** may include a connection fitting **140** for sealingly coupling to tube **500** having a complementary connection fitting **510**. The embodiment depicted in **FIG. 3** may be desirable when hydraulics are use to control movement of the bar within the lumen of the catheter **100**. Referring now to **FIG. 4A**, a schematic illustration of a cut away view of the catheter **100** shown in **FIG. 2** (along line **4-4**) with bar **300** and container **200** disposed within the lumen **150** is shown. Again, catheter **100** has a proximal end **110** and a distal end **120** and a body member **140** defining a lumen **150** extending from the proximal end **100** to the

distal end **120**. The container **200** and bar **300** are slidably disposable in the lumen **150**. In the depicted embodiment, a pushing member **350** is coupled to the bar **300**. The bar **300** and pushing member **350** are positioned in the lumen **150** of the catheter **200** such that the pushing member **350** is capable of engaging the container **200** and pushing the container **200** distally in the lumen **150** when the bar **300** is slid distally in the lumen **150**.

Referring now to **FIGs. 4B-D,** longitudinal cross sections of representative embodiments of catheters **100** are shown. For purposes of illustration, the sections can be considered as being taken along line **4-4** of the catheter **100** depicted in **FIG. 2**. The catheters **100** depicted in **FIGs. 4B-D** have a proximal end **110**, a distal end **120**, and a body member **140** defining a lumen **150** extending from the proximal end **110** to the distal end **120**. A stop feature **400** is positioned in proximity to (e.g., at or near) the distal end **120** of the catheter **100**. The stop feature **400** extends into the catheter lumen **150** and is configured to engage the container **200** to inhibit or prevent the container from exiting the lumen **150** at the distal end **120** of the catheter **100**. It will be understood, as described below with regard to various embodiments, the stop feature **400** is intended to inhibit or prevent the entirety of the container **200** from exiting the lumen **150**, as a portion of the container **200** may exit the lumen **150**. The stop feature **400** may be integrally formed with, bonded to, adhered to, affixed to, or otherwise coupled to the body **140** of the catheter **100**. As shown in **FIG. 4D**, a stop feature **400** may include a piercing element **410** positioned and configured to pierce the container, as described in more detail below with regard to various embodiments.

As shown in **FIG.4C**, a filter **600** or screen may be disposed across the catheter lumen **150** in proximity to the distal end **120**. The filter **600** or screen may prevent unintended particulate matter from exiting the lumen **150** into target tissue of a patient when the catheter is put to use. In the embodiment depicted in **FIG. 4B**, the stop feature **400** may serve as a filter or screen in addition to serving to inhibit or prevent the container from exiting the lumen.

A catheter as described herein may be made of any suitable material or combinations of material. For example, the body of the catheter may be formed from a suitable polymeric material, such as PTFE, ETFE, polyethylene, polypropylene, polycarbonate, or combinations of polymeric materials and may include reinforcing

elements such as braids or meshes. In various embodiments, the catheter may be formed from silicone or polyurethane.

A catheter as described herein may have any suitable dimensions to carryout its intended therapeutic purpose. For example, the catheter is preferably long enough to allow its distal end to be implanted in a target tissue location and to allow its proximal end to be external to the patient. The diameter of the catheter lumen is sized to allow movement of a bar, pushing member if employed, and container within the lumen.

A bar as described herein may be made of any suitable material or combinations of material. When the catheter is flexible and follows a non-linear path through the body of a patient to the target tissue, the bar is preferably sufficiently flexible to follow the non-linear path within the catheter. However, for many therapies, the path that the catheter follows in the patient's body should be substantially linear. In such situations, the bar may be less flexible. In various embodiments, the bar is formed from silicone rubber, butyl rubber, fluorocarbon rubber, neoprene, polyurethane, polyethylene, polypropylene, polytetrafluoroethylene (PTFE), perfluoroalkoxy (PFA), fluorinated ethylene propylene (FEP), ethylene-propylene copolymers,polystyrene, polycarbonate, metals such as stainless steel or nitinol, glass or the like.

A pushing element as described herein may be made of any suitable material or combinations of material. For example, a pushing element may be formed from materials similar to those enumerated above with regard to the bar.

A piercing element as described herein may be made of any suitable material or combinations of material. In various embodiments, the piercing element is formed from a rigid polymeric material, such as polystyrene, high density polyethylene, polycarbonate, or the like.

A filter as described herein may be made of any suitable material or combinations of material. For example, a pushing element may be formed from materials similar to those enumerated above with regard to pushing member.

Referring now to **FIGs. 5-6**, schematic illustrations of cross sections of representative containers **200** are shown. In the embodiment depicted in **FIG. 5A**, the container **200** includes a housing **210** defining a reservoir **220** for containing a biologic agent. In various embodiments, the wall is formed from an elastomeric material and the volume of the reservoir **220** is variable. In numerous embodiments, the housing **210** is

sufficiently stiff to maintain its shape to ensure proper slidability within a lumen of a catheter of a delivery system. Regardless of the degree of stiffness of housing **210**, the container **200** is configured such that force applied to one face (e.g., in the direction of line **F**), or a portion thereof, of the container **200**, while the opposing face is substantially stationary, causes the face on which force is exerted to move towards the opposing stationary face to force contents out of the reservoir. In various embodiments, the housing **210** is configured to be piercable by a piercable element, to allow contents of the reservoir **220** to escape, and in some embodiments, to reduce internal reservoir pressure so that such pressure does not overcome force **F**.

In the embodiment depicted in **FIG. 5B**, a rupturable membrane **250** sealingly engages the interior perimeter of a wall **212** of the housing **210** such that the rupturable membrane **250** and the housing together define the reservoir **220** for containing a biologic agent. While not shown, it will be understood that rupturable membrane **250** may sealingly engage an exterior perimeter of the wall **212**. The membrane **250** may be bonded, adhered, affixed or otherwise attached or sealingly engaged to the wall **212**. The rupturable membrane **250** may be piercable by a piercable element of a catheter of a delivery system, may rupture upon increased pressure (e.g., when force **F** is applied), may include a line of weakening along which the rupture may occur, or the like. In various embodiments, the rupturable membrane **250** is a self sealing septum that allows introduction of the biologic agent into the reservoir **220** via a needle (not shown) and sealingly contains the biologic agent upon withdrawal of the needle.

Referring now to **FIGs. 6A-B**, container **200** includes a body member **210** having a proximal end **202** and a distal end **204**. The body member **210** defines a lumen extending from the proximal end **202** to the distal end **204**. The container further includes a sealing element **230** slidably disposable within the lumen of the container **200**. The sealing element **230** is configured to sealingly engage the body member **210** as the element **230** is slid within the lumen. In the depicted embodiment, the sealing element **230** includes an O-ring **235** for sealingly engaging the body member **210** within the lumen. Of course, sealing element **230** may form a seal in any suitable manner. For example, sealing member may include wiper seals or the like. A rupturable membrane **250** is disposed across the lumen in proximity to the distal end **204** of the body member **200**. A reservoir

220 for containing a biologic agent is formed between the rupturable membrane **250**, the sealing element **230** and the body member **210.**

The housing of the container may be made of any suitable material. For example, the housing, or portions thereof, may be formed from, glass, silicanized stainless steel, silicanized titanium, nitinol, polystyrene, polyethylene, polycarbonate, ethylene vinyl acetate, polypropylene, polysulfone, polymethylpentene, polytetrafluoroethylene (PTFE) or compatible fluoropolymer, a silicone rubber or copolymer, poly(styrene-butadiene-styrene), polyurethane or the like, or a combination thereof. In various embodiments, the housing is made of polyurethane. It will be appreciated that the material of choice and thickness of the housing may be varied depending on the whether an elastic or rigid housing is desired.

Body (as shown in **FIGs. 6A-B**) may be formed of any suitable material. For example, body member may be formed of the same or similar materials as those described above with regard to a rigid housing.

Surfaces of the housing or other portions of a container that may come into contact with the biologic agent may be treated or coated to improve compatability with the biologic, reduce adherence of the biologic agent, or the like.

Rupturable membrane may be made of any suitable material, such as those enumerated above with regard to housing. In some embodiments, where rupturable membrane is a sealable septum, the membrane is made from a suitable elastomeric material, such as silicone rubber, butyl rubber, flurorcarbon rubber, polyethylene, polypropylene, polytetrafluoroethylene (PTFE) or the like. In many embodiments, the membrane is permeable to atmospheric gasses but is impermeable to aqueous liquids. In such embodiments, the membrane may be formed from polystyrene, polycarbonate, ethylene vinyl acetate, polysulfone, polymethylpentene, polytetrafluoroethylene (PTFE) or compatible fluoropolymer, a silicone rubber or copolymer, poly(styrene-butadiene-styrene), or polyolefin, such as polyethylene or polypropylene, or combinations of these materials. It will be understood that desired thickness may vary depending on the material from which the membrane is formed. By way of example, the membrane may be between about 0.02 millimeters and 0.8 millimeters thick.

Sealing member (moveable wall) may be formed from any suitable material. If the sealing member is a one-piece element formed from a single material, sealing member

may be formed from a suitable elastomeric material, such as silicone rubber, butyl rubber, flurorcarbon rubber, neoprene, polyurethane, polyethylene, polypropylene, polytetrafluoroethylene (PTFE), perfluoroalkoxy (PFA), fluorinated ethylene propylene (FEP), ethylene-propylene copolymers, or the like If sealing element includes a separate sealing feature, such as an O-ring, wiper seal , or the like, the non sealing feature of the sealing element may be formed, for example, materials as enumerated above with regard to housing.

In various embodiments, the housing, sealing member, and rupturable membrane are all made of the same material to reduce the number of materials that the therapeutic agent contacts. For example, the housing, sealing member, and rupturable membrane may all be formed from polyurethane.

Referring now to **FIGs. 7-11**, longitudinal cross sections of some components of representative delivery systems **1000** are shown. In the various embodiments depicted in **FIGs. 7-11**, a container **200** is slidably disposed in a lumen **150** of a catheter **100**. A bar **300** including a distally located pushing element **350** is slidably disposed in the lumen **150**. The container **200** is positioned in the lumen **150** distally relative to the bar **300** and pushing element **350**. As the bar **300**, **500** is slid distally in the lumen **150**, the pushing element **350, 550** engages the container **200** and causes the container **200** to slide distally in the lumen **150**. Stopping feature(s) **400** located in proximity to (i.e., generally at or near) the distal end **120** of body member **140** inhibit or prevent container **200**, or a portion thereof, from exiting the lumen **150** of the catheter **100**. When the stop feature(s) **400** engage the container **200**, further distal movement of bar **300, 500** in lumen forces the contents (not shown) of the container **200** out of the container **200** and out of the distal end of the lumen **150**.

In the embodiment depicted in **FIGs. 7A-D**, piercing element **410** pierces a portion of the face of the container housing **210'** facing the distal end **120** of the catheter body **140** as the container moves distally in the catheter lumen **150**. Further distal movement of bar **300** in lumen **150** forces contents (not shown) out of the container **200** and out of the distal end of the lumen **150** through the pierced region. In addition, the side walls **210''**, **210'''** of the container housing collapse as the bar is moved distally when the container **200** engages the stop feature **400** (see **FIG. 7D**). The side walls **210''**, **210'''** may be in the form of a bellows, may be sufficiently deformable to collapse, or the like. In various

embodiments (not shown), the piercing element **410** may be a needle advanced distally through the lumen **150** of the catheter **100** and through the container **200**. For example, the needle (not shown) may be inserted through a lumen (not shown) of the bar **300**. The needle may have an etched surface for piercing the container **200** or may have a surface that is covered with an array of microneedles to allow for more spreadout distribution of the agent.

As further shown in **FIG. 7D**, a screen **600** or filter may be disposed in the catheter lumen **150** in proximity to the distal end **120** to inhibit or prevent unintended particulate matter, such as parts of the container housing **210**, from exiting the lumen **150**. As further shown in the embodiment depicted in **FIGs. 7A-D**, pushing element **350** includes a sealing element **355**, such as an O-ring, so that pushing element **355** sealingly engages body **140** in lumen **150**. By sealingly engaging body **140** in lumen **150**, pushing element **350** can inhibit or prevent contents that leave container **200** from moving proximally in the lumen **150**. In various embodiments, pushing element **350** does not sealingly engage body **140** of catheter **100**.

Referring now to **FIGs. 8A-C**, a container **200** similar to that depicted in and discussed with regard to **FIGs. 6A-B** is shown disposed in catheter lumen **200** distally to bar **300**. The bar **300** is slidably disposed in lumen **510** a second bar **500**, which is slidably disposed in the lumen **150** of the catheter **100**. The second bar **500** includes a body member **520** that defines the lumen **510**. The second bar **500** includes a pushing member **550** at the distal end of the bar **500**. The second pushing member **550** includes an opening **530** axially aligned with the lumen **512**. The first bar **300** is axially slidable in the lumen **510** of the second bar **500** and extendable beyond the opening **530**. The second pushing member **550** is configured to engage the container **200** and move the container **200** distally in the catheter lumen **150** as the second bar **500** slides distally in the catheter lumen **150**. The second bar **500** pushes the container **200** distally in the catheter lumen **150** until the container **200** engages stop feature **400**. If the second bar **500** is moved manually within the catheter lumen **150**, tactile feedback that the container **200** has engaged the stop feature **400** may indicate to the user that no further distal pushing of the bar **500** is desirable. If the bar **500** is moved via an automated mechanism, feedback, such as increased resistance to movement, increased pressure on stop feature, increased power

consumption without further movement or the like may be used to indicate that further distal movement of the bar **500** should be ceased.

In the embodiment depicted in **FIGs. 8A-C**, distal movement of the second bar **500** causes distal movement of the first bar **300**, as the second pushing element **550** engages the first pushing element **350** and pushes the first pushing element **350** distally as the second bar **500** is slid distally in catheter lumen **150**. At a point where the second bar **500** is pushed distally such that the container **200** engages stop feature **400**, the first bar **300** may be moved distally to force contents (not shown) out of the container **200** and out of the catheter **100**. In the embodiment shown, the pushing element **350** of the first bar **300** is configured to engage the moveable sealing member **230** of the container **200**. As the first bar **300** is moved distally when the container **200** is engaged with stop feature **400**, the pushing element **350** moves the sealing member **230** distally forcing contents out of container **200** via rupturable membrane **250**. While not shown, it will be understood that a filter or screen may be disposed across the catheter lumen **150** (e.g., as shown in **FIGs.7-D**).

Referring now to **FIGs. 9A-B**, an embodiment similar to that shown in **FIGs. 8A-C** is shown, with like numbers referring to like parts. In the embodiment shown in **FIGs. 9A-B**, the stop feature **400** includes piercing elements **410**. When the container **200** is pushed distally in catheter lumen **150** such that the container **200** engages the stop feature **400**, piercing element **410** pierces rupturable membrane **250**. As the sealing member **230** is moved distally, contents of the container **200** can exit via the pierced portion of the membrane **250**.

Referring now to **FIGs. 10A-C**, an embodiment similar to that shown in **FIGs. 8A-C** is shown, with like numbers referring to like parts. In **FIG. 10**, container **200** includes a tapered distal region configured to extend beyond the distal end **120** of the catheter **100** when the stop feature **400** engages the container **200**. In various embodiments, the distal tapered region of the container **200** has a sufficiently large inner diameter to avoid subjecting the contents of the container **200** to shear stress as the contents are forced through the distal tapered region. As shown in **FIG. 10**, the sealing member **230** of the container **200** may be sized and shaped in a similar manner to the distal tapered region to increase the amount of contents that may be forced out of the container **200**.

Referring now to **FIG. 11**, a bar **300** or pushing member **350** of the bar may serve as a sealing member of a container. In the depicted embodiment, pushing member **350** sealingly engages the body of the container as the pushing member **350** is moved distally within the container to force contents out of the container.

While not shown, it will be understood that mechanisms other than bars **300**, **500** may be used to move container **200** distally in lumen **150** and force contents out of the container **200**. For example, air pressure or hydraulic fluid pressure (e.g., saline) may be used to move the container **200** and provide force to release contents. In such embodiments, it may be desirable for the container **200** to sealingly engage the body **140** of the catheter **100**. It will be further understood that a bar **300**, **500** may be moved in the lumen **150** by any suitable mechanism, such as hydraulic fluid pressure, air pressure, motor, manually, or the like.

Referring now to **FIGs. 12-14**, block diagrams of some representative components of automated systems for moving bars as discussed above within lumens of catheters are shown. In the simple form shown in **FIG. 12**, such a system may include a controller **2100**, a driving mechanism **2200**, and a bar **300**. Any suitable controller **2100**, such as a microprocessor, may be employed to control the driving mechanism **2200**. Any suitable driving mechanism **2200** may be employed to move bar **300**. In various embodiments, the driving mechanism **2200** is a motor, such as a stepper motor. In some embodiments, the driving mechanism **2200** is a hydraulic or air pressure driving mechanism. In such embodiments, the bar **300** preferably sealingly engages the body of the catheter to prevent hydraulic fluid from leaking in the lumen distal to the bar **300**. As shown in **FIGs. 13-14**, in embodiments where first **300** and second **500** bars are employed, a single drive mechanism **2200** may be used to drive both bars **300**, **500** or a first drive mechanism **2210** may be used to move the first bar **300** and a second drive mechanism **2220** may be used to move the second bar **500**.

Referring now to **FIGs. 15-22**, schematic illustrations of various configurations of containers **200** useful in delivery systems as described above are shown. In **FIG. 15**, a schematic longitudinal cross section of a container **200** is shown. The container **200** includes a sealing element **230** and a rupturable membrane **250**. The rupturable membrane **250** may be a self sealing septum to allow contents to be added to the container **200**. The sealing element **230** includes a piercing element **290** configured to pierce rupturable

membrane **250** to allow contents to exit the container **200** when the sealing member **230** is moved distally. As shown in the schematic side view of **FIG. 16**, a container **200** may include first **260** and second **270** connectable portions. The second portion **270** may serve as a removable and resealable cap. The cap may be removed so that contents may be added to the first portion **260** and resealed to prevent the contents of the container **200** from leaking or spilling. The first **260** and second **270** portions include complementary mating features **261**, **271** to allow disconnecting and reconnecting of the first and second parts. In the depicted embodiment, the first portion **260** includes external threads **261**. The second portion **270** includes complementary internal threads **271** (represented by internal dashed lines). Of course, any other suitable form of connection may be employed. As shown in **FIGs. 17A-B**, which is similar to the embodiment depicted in **FIG. 16** with like numbers referring to like parts, the second portion **270** of the container **200** may include a rupturable membrane **250**. In the embodiment depicted in **FIG. 18**, the first part **260** includes a sealing element **230** and the second part **270** includes a rupturable membrane **250**.

Referring now to **FIG. 19**, container **200** may include an outer sheath **280** that surrounds the housing **210** of the container. In various embodiments, the outer sheath **280** may be removed in the operating room prior to insertion of the container **200** into the lumen of a catheter of a delivery system. The sheath **280** may thus prevent excessive exposure (and thus contamination) of the housing **210** prior to delivery of its contents. In some embodiments, the outer sheath **280** may be removable following insertion into the catheter so that physician contact with the inner housing **210** is prevented. Of course, the outer sheath **280** and housing **210** may be ruptured in proximity to the distal end of the catheter as the agent disposed in the housing is released. In various embodiments, the outer sheath **280** is permeable to atmospheric gases, but impermeable to aqueous liquids. Such breathable outer sheaths **280** may be desirable when the container **200** houses cells and it is desirable to preserve the viability of the cells prior to delivery.

Referring now to **FIG. 20**, a container **200** may be sealingly subdivided into first **298** and second chambers **299**. The first **298** and second **299** chambers may house different agents that may not be compatible if stored together. In various embodiments, the first chamber **298** houses a fluoroscopic medium to enable visualization via imaging techniques and the second chamber **299** houses a biologic agent. Just prior to introduction

into a patient through the use of a delivery system as described above, the contents of the first **298** and second **299** chambers may be mixed. **FIGs. 21-22** depict schematic longitudinal cross sections of two embodiments of such two-compartment containers.

In the embodiment depicted in **FIG. 21**, the container **200** includes first **260**, second **270**, third **260'** and fourth **270'** parts. The first **260** and second **270** parts include complementary mating features **261, 271** to allow for disconnection and sealing reconnection. The first **260** and second **270** parts together form the first chamber **298** of the container **200**. A first material may be disposed in the first part **260** and the second part **270** may be connected to the first part **260** to seal the material in the first chamber **298**. A rupturable membrane **250** prevents the material from exiting the sealed first chamber **298**. The third part **260'** includes a complementary mating feature **261'** to a mating feature **271'** of the second part **270** to allow for disconnection and sealing reconnection. The second **270**, third **260'**, and fourth **270'** parts together form the second chamber **299**. The third part **260'** includes a complementary mating feature **261''** to a mating feature **271''** of the fourth part **270'** to allow for disconnection and sealing reconnection. When the second **270** and third **260'** parts are connected, a second material may be introduced in the third part **260'**. The fourth part **270'** may then be sealingly connected to the third part **260'**. The fourth part **270'** includes a rupturable membrane **250'** to prevent the contents of the second chamber **299** from leaking or spilling. The rupturable membrane **250** prevents interaction between the contents of the first **298** and second **299** chambers during storage. Upon rupture of the membrane **250** in use, the contents of the first **298** and second chambers **299** can mix.

In the embodiment depicted in **FIG. 22**, the container **200** includes first **260**, second **260'**, and third **270'** parts. The first **260** and second **260'** parts include complementary mating features **261, 271** to allow for disconnection and sealing reconnection. The first **260** and second **270** parts together form the first chamber **298** of the container **200**. A first material may be disposed in the first part **260** and the second part **270** may be connected to the first part **260** to seal the material in the first chamber **298**. A rupturable membrane **250** prevents the material from exiting the sealed first chamber **298**. The third part **270'** includes a complementary mating feature **271'** to a mating feature **261'** of the second part **260'** to allow for disconnection and sealing reconnection. The second **260'** and third **270'** parts together form the second chamber

299. A second material may be introduced in the second part **260'**. The third part **270'** may then be sealingly connected to the second part **260'**. The third part **270'** includes a rupturable membrane **250'** to prevent the contents of the second chamber **299** from leaking or spilling. The rupturable membrane **250** prevents interaction between the contents of the first **298** and second **299** chambers during storage. Upon rupture of the membrane **250** in use, the contents of the first **298** and second chambers **299** can mix.

In the embodiments depicted in **FIGs. 21-22**, the moveable sealing member includes a tapered distal region that may serve as a piercing element to facilitate rupturing membranes **250**, **250'**.

While not described at length herein, it will be understood that the biologic agent to be delivered may be delivered in any form, e.g. liquid or solid. By using a system as described herein, solid forms and liquid forms of the biologic agent should be readily interchangeable without the need to design and develop new catheters or components of the system. Examples of suitable solid forms of biologics that may be delivered in accordance with the teachings provided herein include lyophilized particles or solid scaffolds. In many circumstances, solid scaffolds are considered more effective for delivering therapy to a highly vascularized region such as the myocardium.

The various embodiments shown and described herein include various components. One of skill in the art will readily understand that components of a given described embodiment may be readily substituted for, or used in addition to, components of a different described embodiment.

Thus, embodiments of the SYSTEM AND METHOD FOR DELIVERY OF BIOLOGIC AGENTS are disclosed. One skilled in the art will appreciate that the present invention can be practiced with embodiments other than those disclosed. The disclosed embodiments are presented for purposes of illustration and not limitation, and the present invention is limited only by the claims that follow.

What is claimed is:

1. A container for housing a therapeutic agent, comprising:
a body member having a proximal end and a distal end and a lumen extending from the proximal end to the distal end;
a sealing element slidably disposable in the lumen, wherein the sealing element is configured to sealingly engage the body member as the element is slid within the lumen;
a first rupturable membrane disposed across the lumen in proximity to the distal end of the body member,
wherein a reservoir for housing the therapeutic agent is formed in the lumen between the sealing element and the rupturable membrane.

2. The container of claim 1, wherein the membrane is configured to rupture due to increased pressure in the lumen caused by distal movement of the sealing element in the lumen.

3. The container of claim 2, wherein the rupturable membrane comprises a line of weakening configured to rupture due to the increased pressure.

4. The container of claim 1, further comprising a sheath surrounding the body member.

5. The container of claim 4, wherein the sheath is configured to be permeable to atmospheric gases and impermeable to aqueous liquids.

6. The container of claim 1, wherein the container further includes a piercing element and wherein the membrane is configured to rupture upon being pierced by the piercing element.

7. The container of claim 6, wherein the sealing element includes the piercing element.

8. The container of claim 1, wherein the container is generally cylindrical.

9. The container of claim 1, wherein the body member comprises first and second removable and resealable parts having complementary mating features, wherein when sealingly engaged the first and second parts together form the lumen.

10. The container of claim 9, wherein the first part includes the sealing element.

11. The container of claim 10, wherein the second part includes the rupturable membrane.

12. The container of claim 9, wherein the second part includes the rupturable membrane.

13. The container of claim 1, further comprising a second rupturable membrane disposed in the lumen and sealingly dividing the reservoir into first and second chambers.

14. The container of claim 13, wherein the body member comprises first, second, and third detachable and resealable parts,
wherein the first and second parts have complementary mating features configured to allow the first and second parts to be detached and resealingly engaged,
wherein the second and third parts have complementary mating features configured to allow the second and third parts to be detached and resealingly engaged, and
wherein when sealed the first, second and third parts together form the lumen.

15. The container of claim 14, wherein the first part includes the sealing element.

16. The container of claim 14, wherein the second part includes the second rupturable membrane.

17. The container of claim 14, wherein the third part includes the first rupturable membrane.

18. The container of claim 14, wherein the first part includes the sealing element, wherein the second part includes the second rupturable membrane, and wherein the third part includes the first rupturable membrane.

19. The container of claim 13, wherein the body member comprises first, second, third and fourth detachable and resealable parts,
wherein the first and second parts have complementary mating features configured to allow the first and second parts to be detached and resealingly engaged,
wherein the second and third parts have complementary mating features configured to allow the second and third parts to be detached and resealingly engaged,
wherein the third and fourth parts have complementary mating features configured to allow the third and fourth parts to be detached and resealingly engaged, and
wherein when sealed the first, second, third and fourth parts together form the lumen.

20. The container of claim 19, wherein first part includes the sealing element, the second part includes the second rupturable membrane, and the fourth part includes the first rupturable membrane.

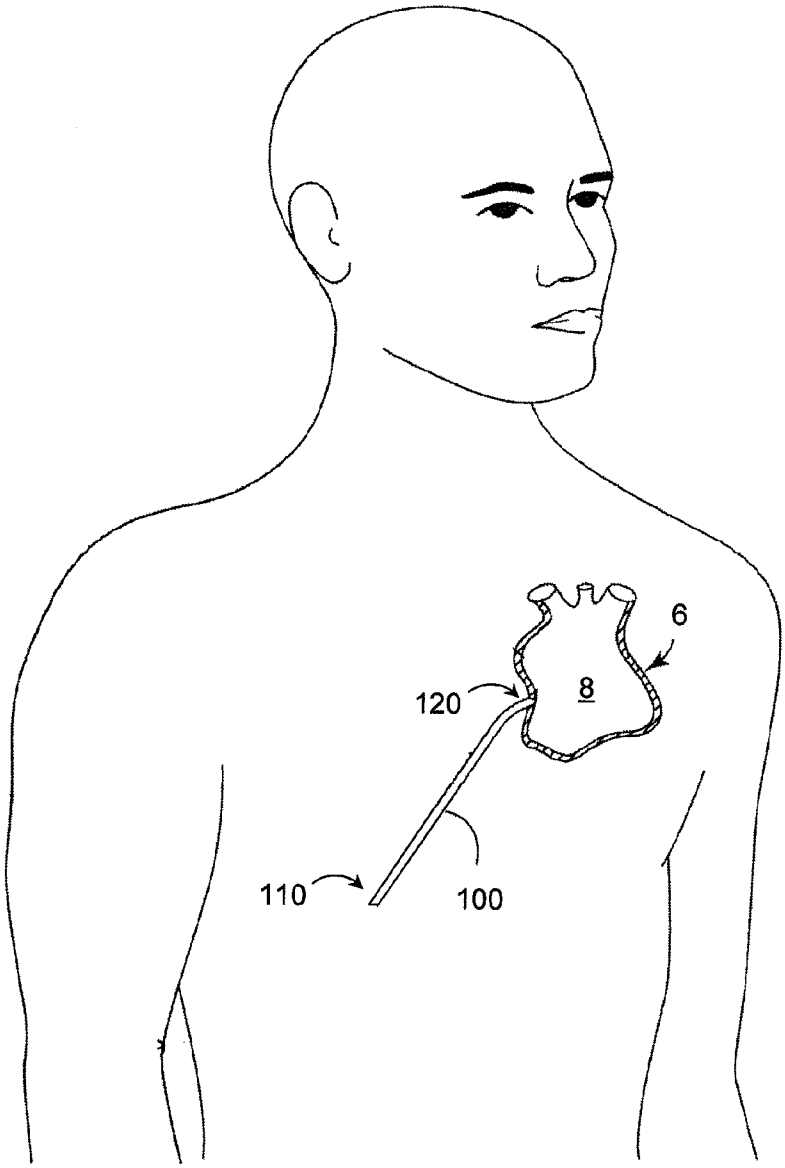

FIG. 1

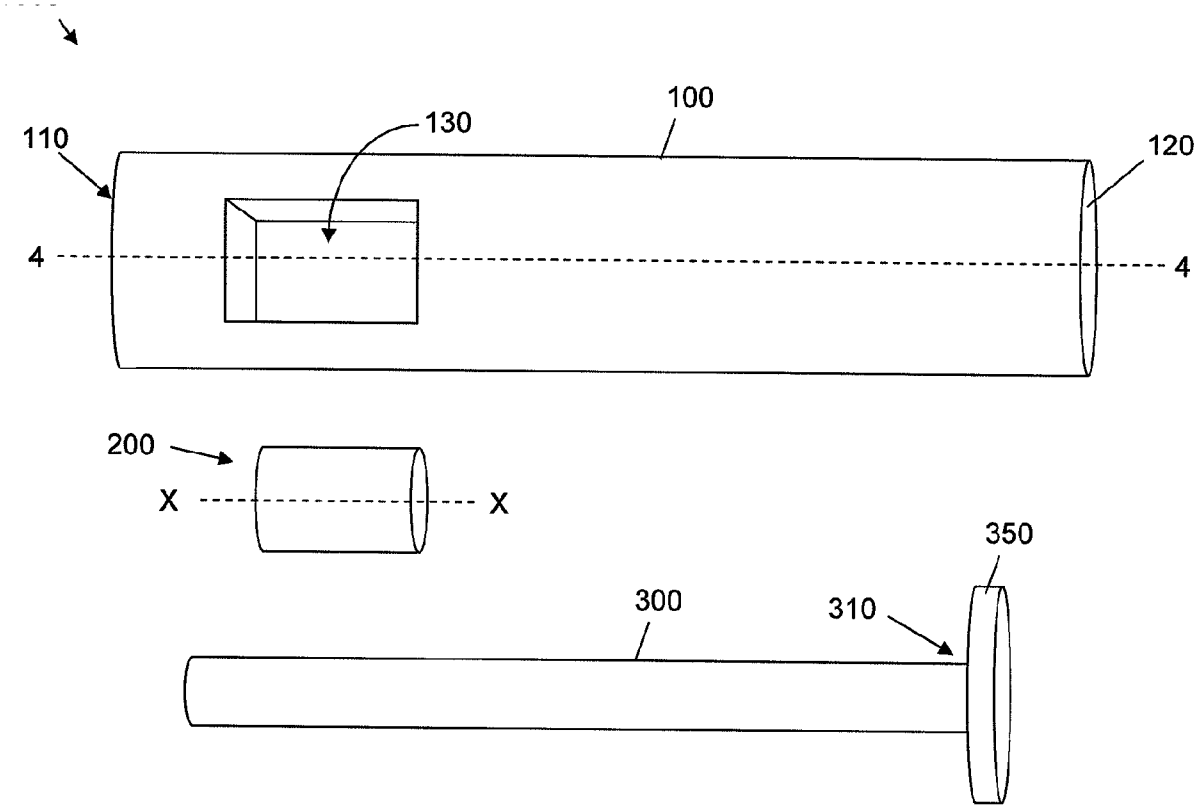

FIG. 2

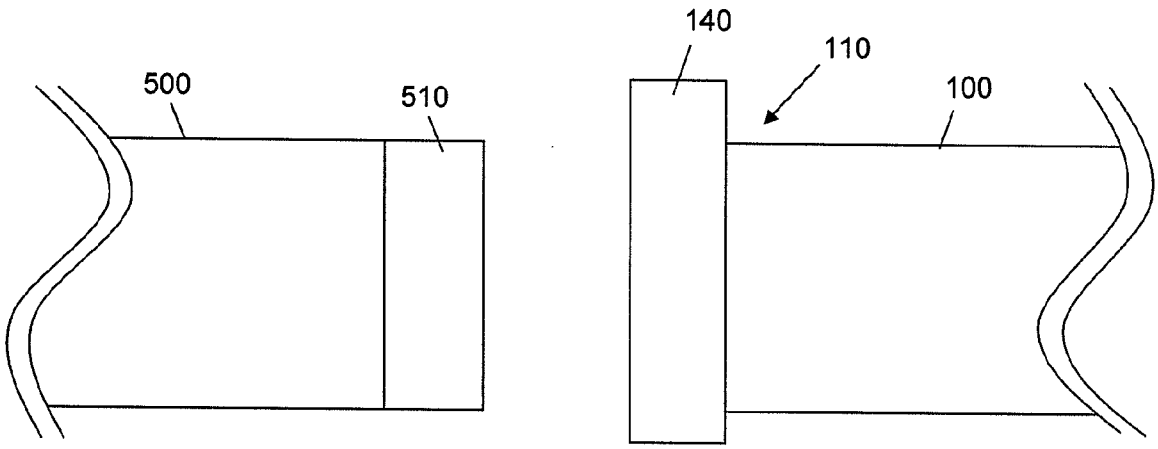

FIG. 3

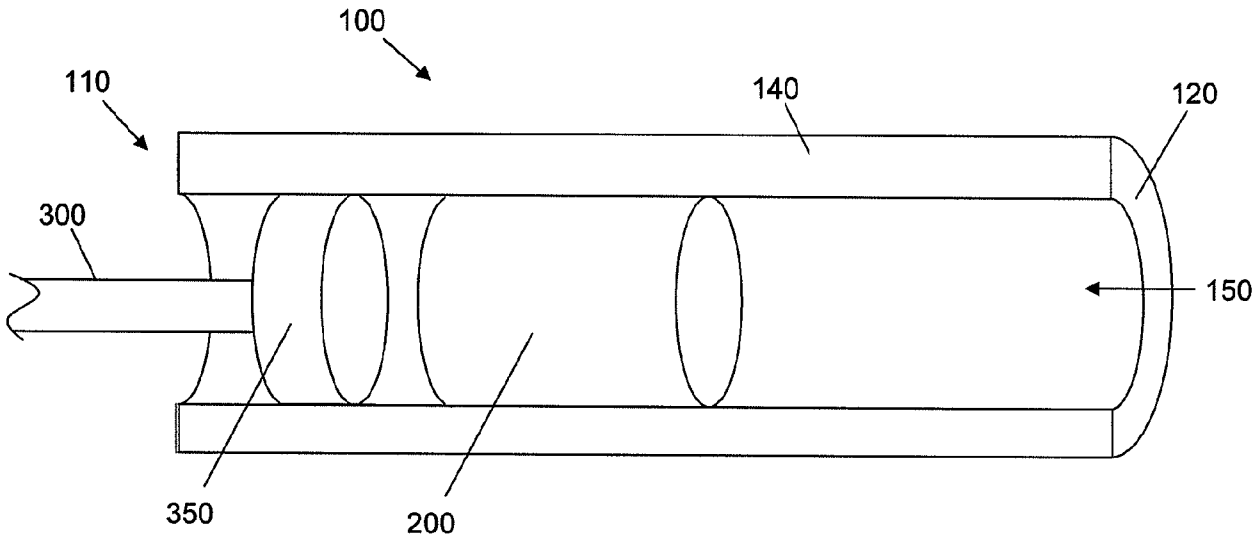

FIG. 4A

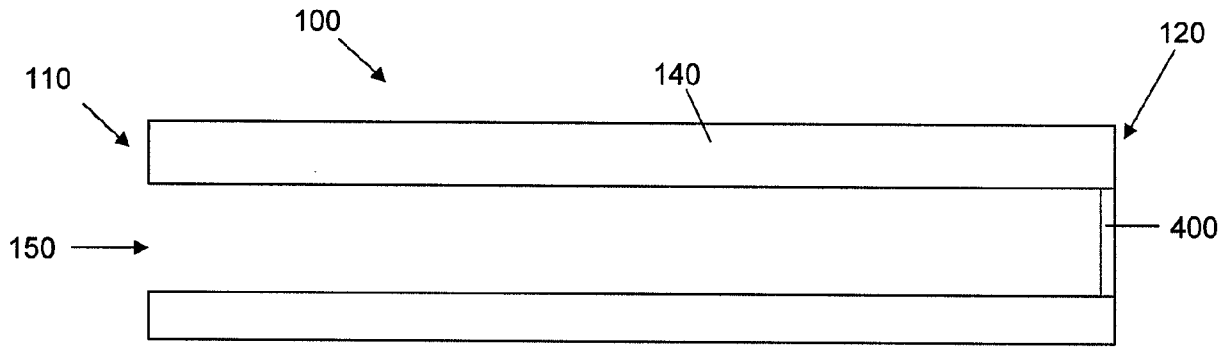

FIG. 4B

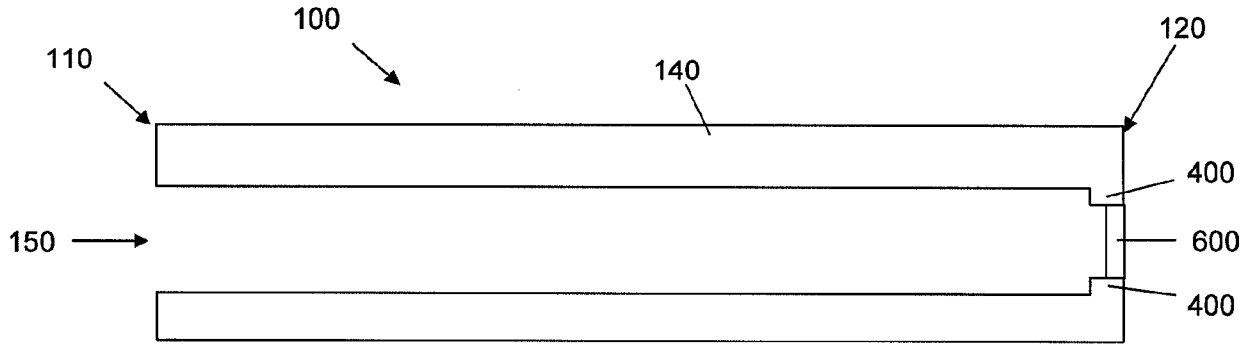
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FIG. 4C

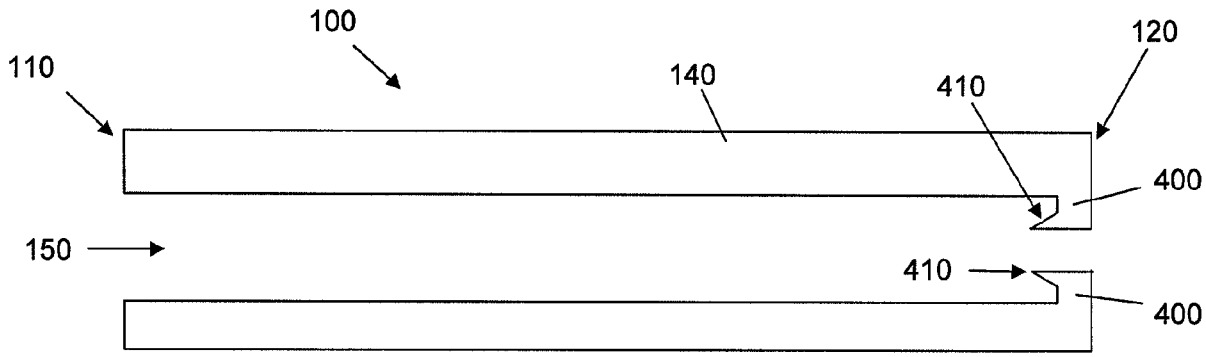
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FIG. 4D

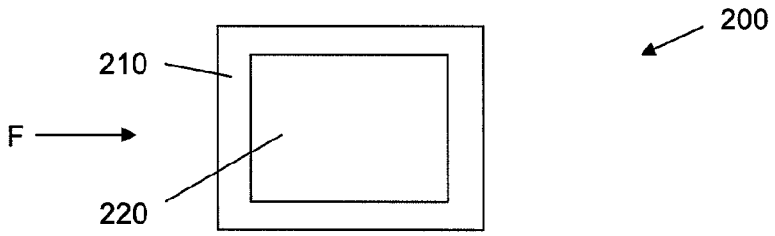

FIG. 5A

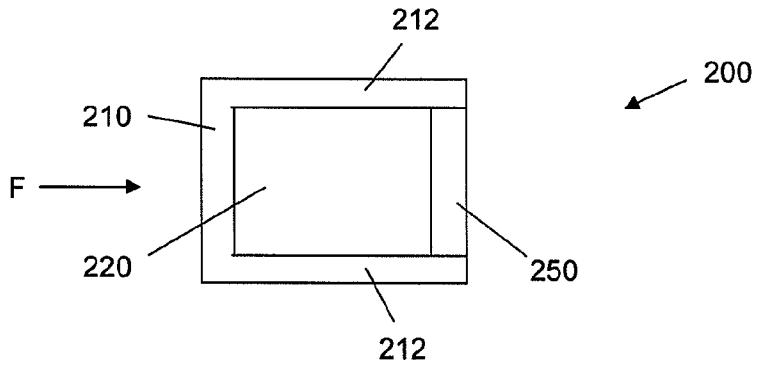

FIG. 5B

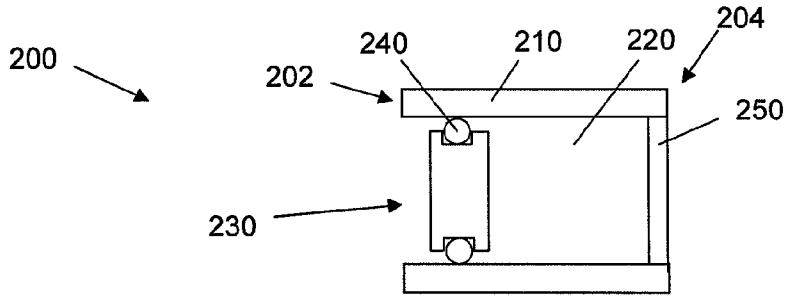

FIG. 6A

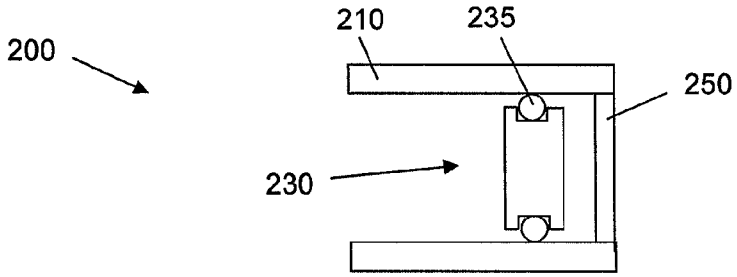

FIG. 6B

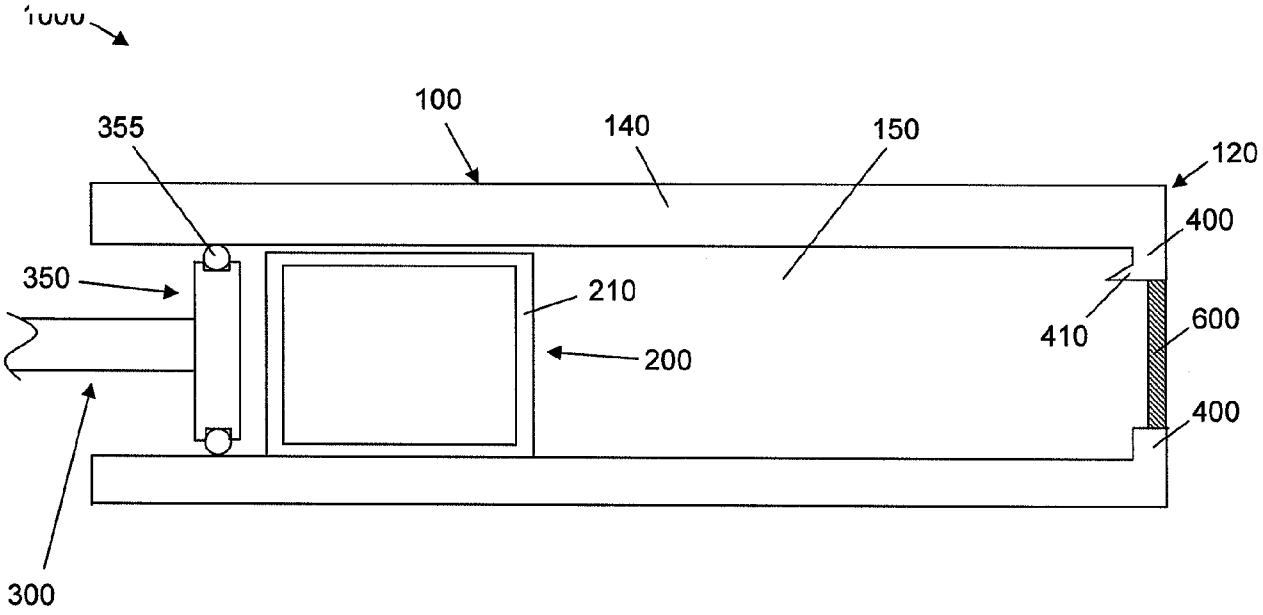
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FIG. 7A

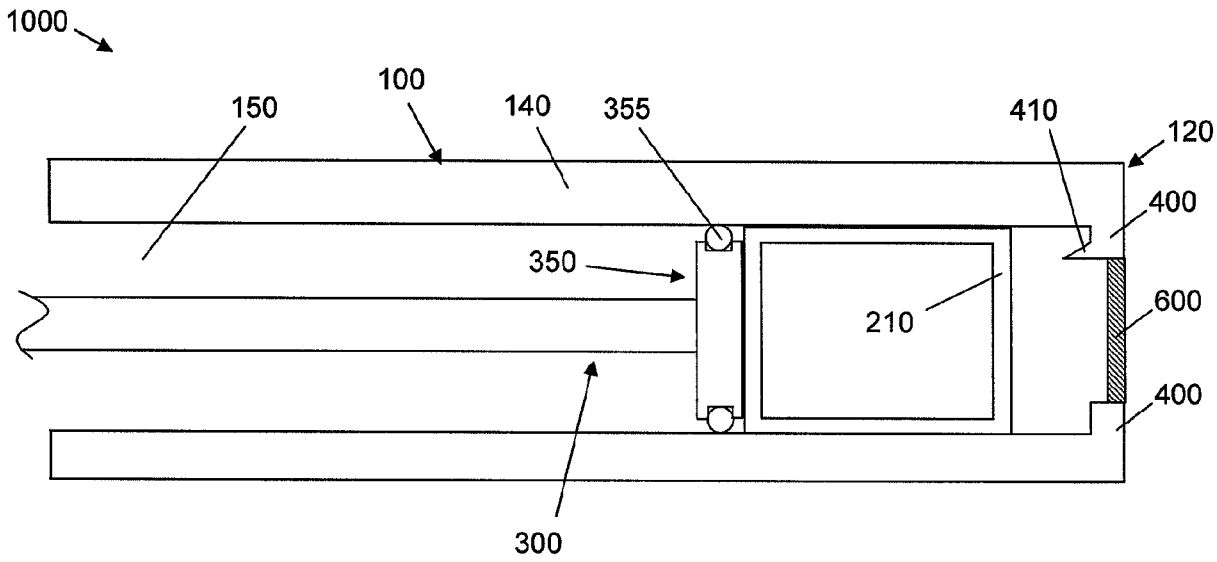
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FIG. 7B

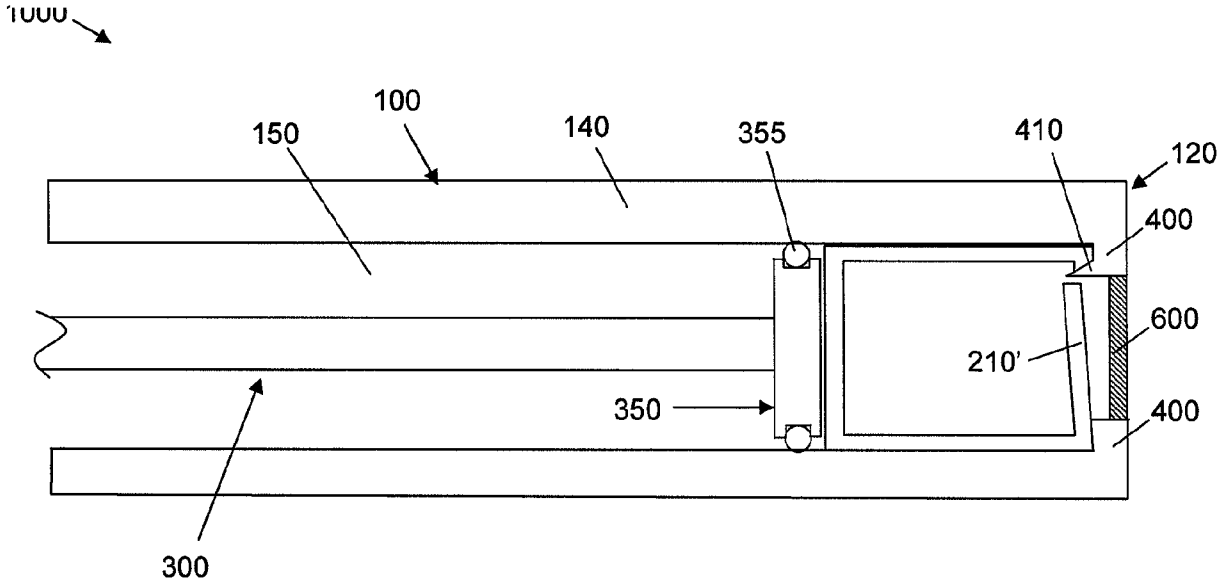
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FIG. 7C

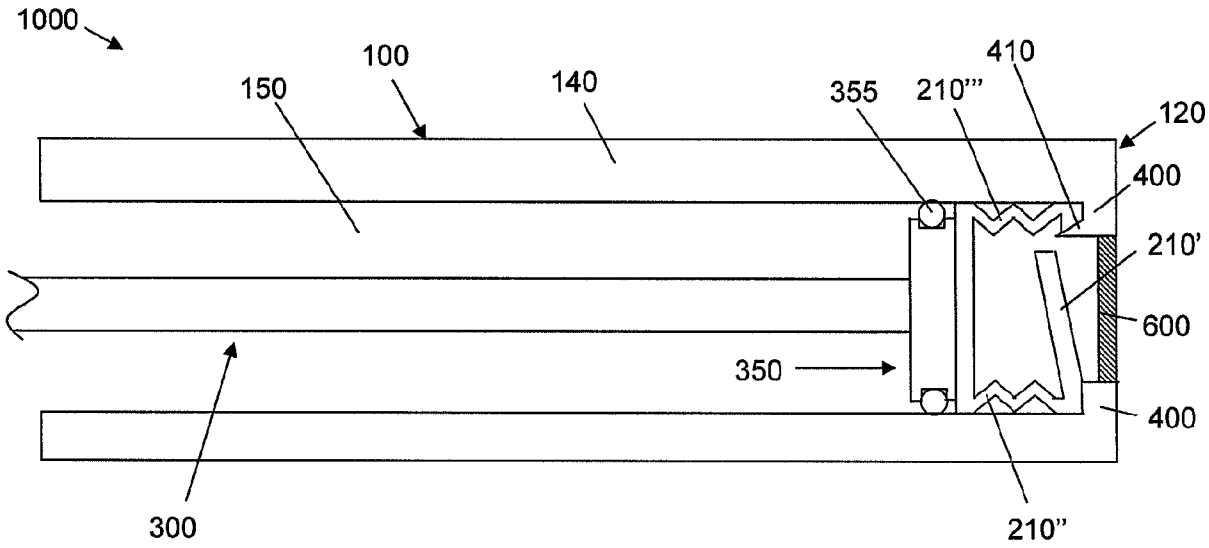
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FIG. 7D

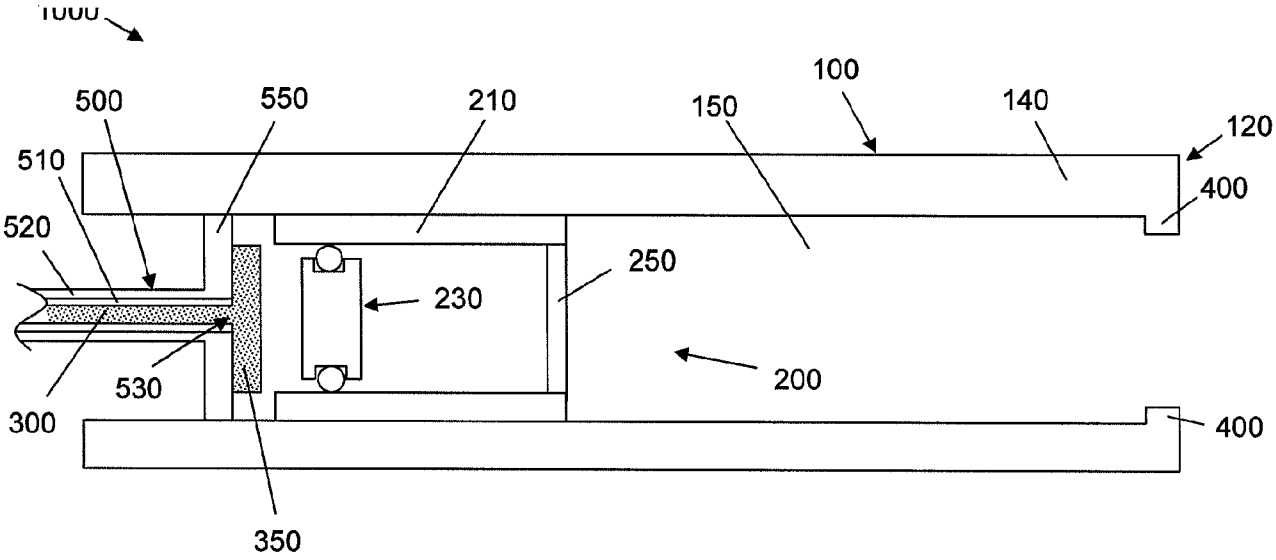
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FIG. 8A

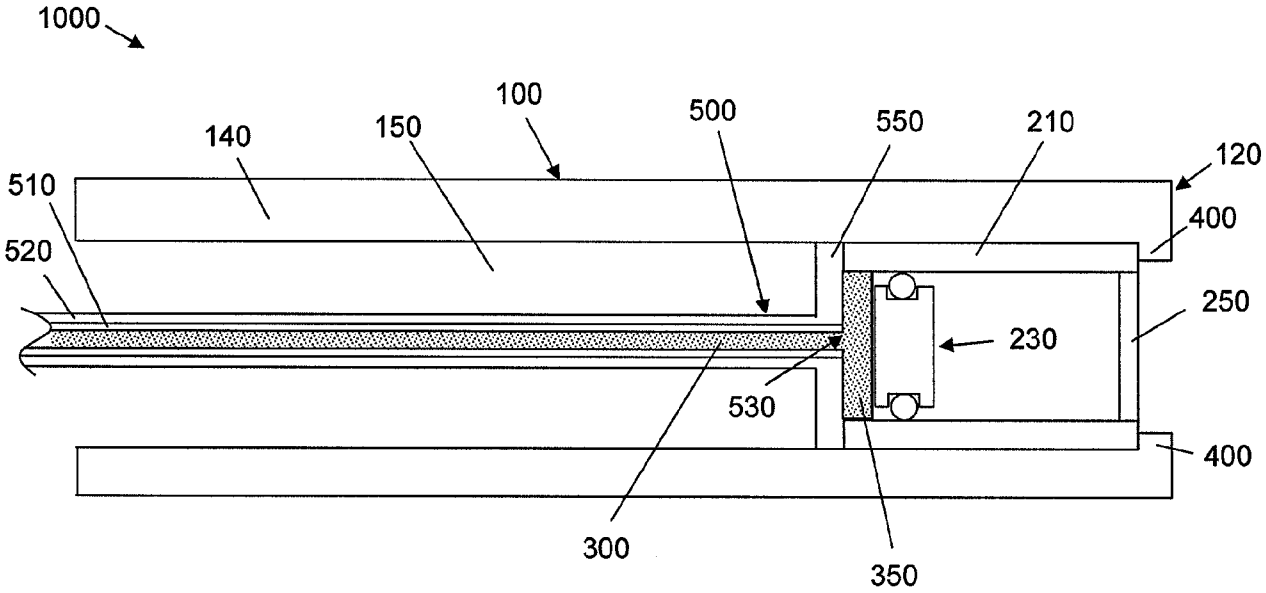
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FIG. 8B

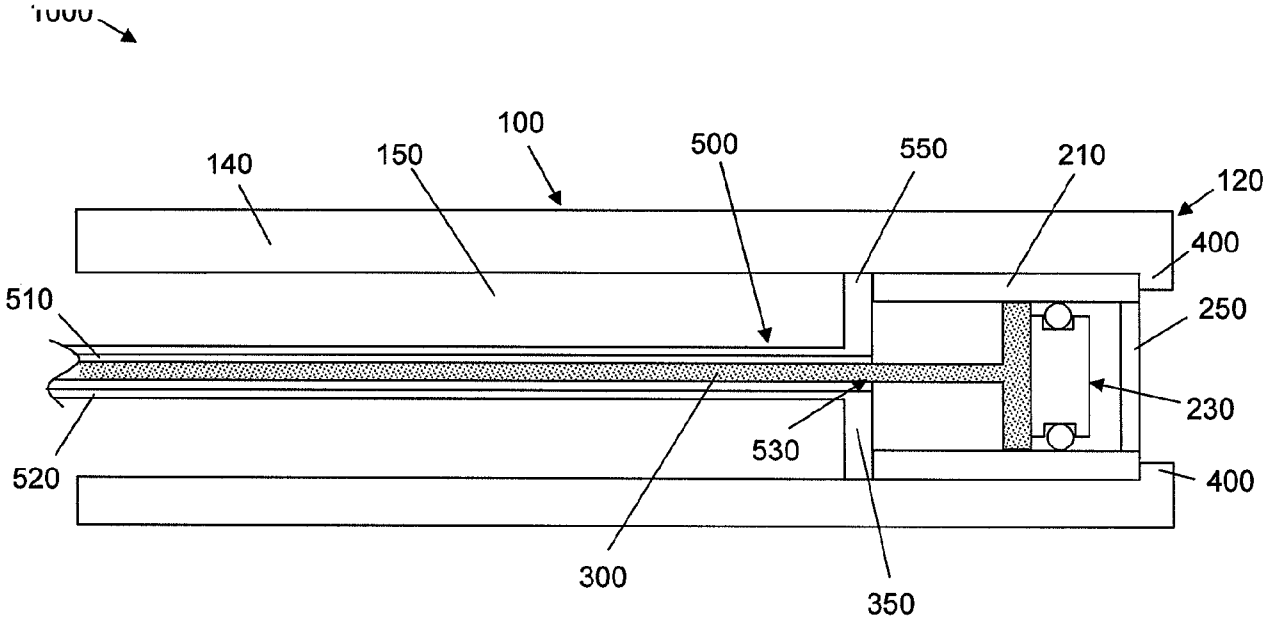
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FIG. 8C

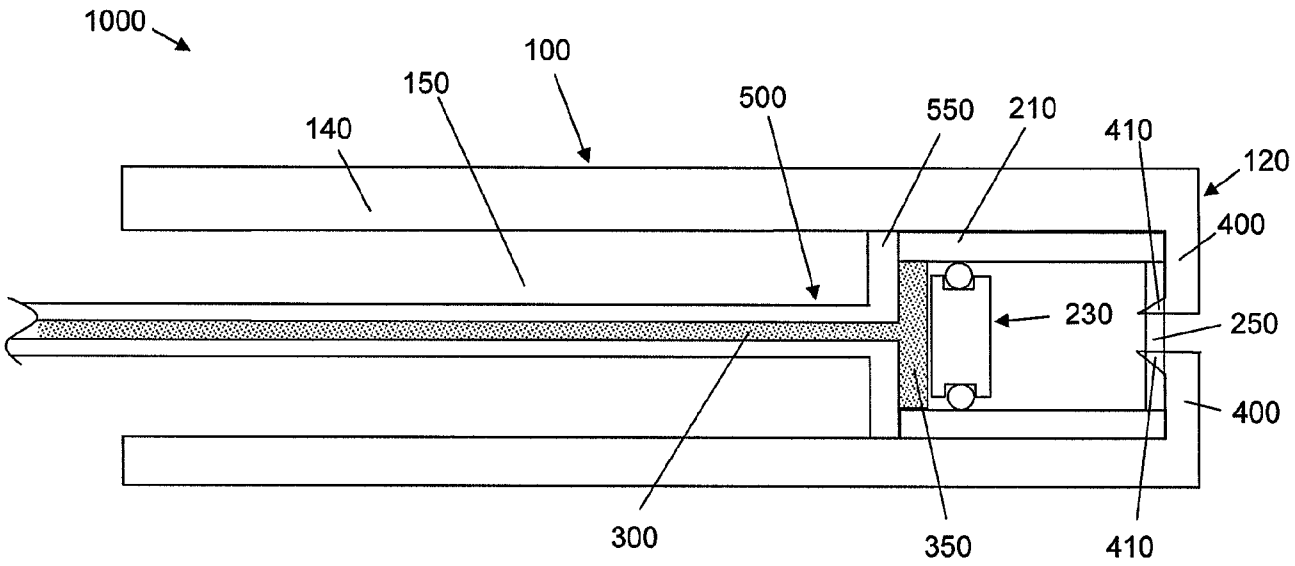
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FIG. 9A

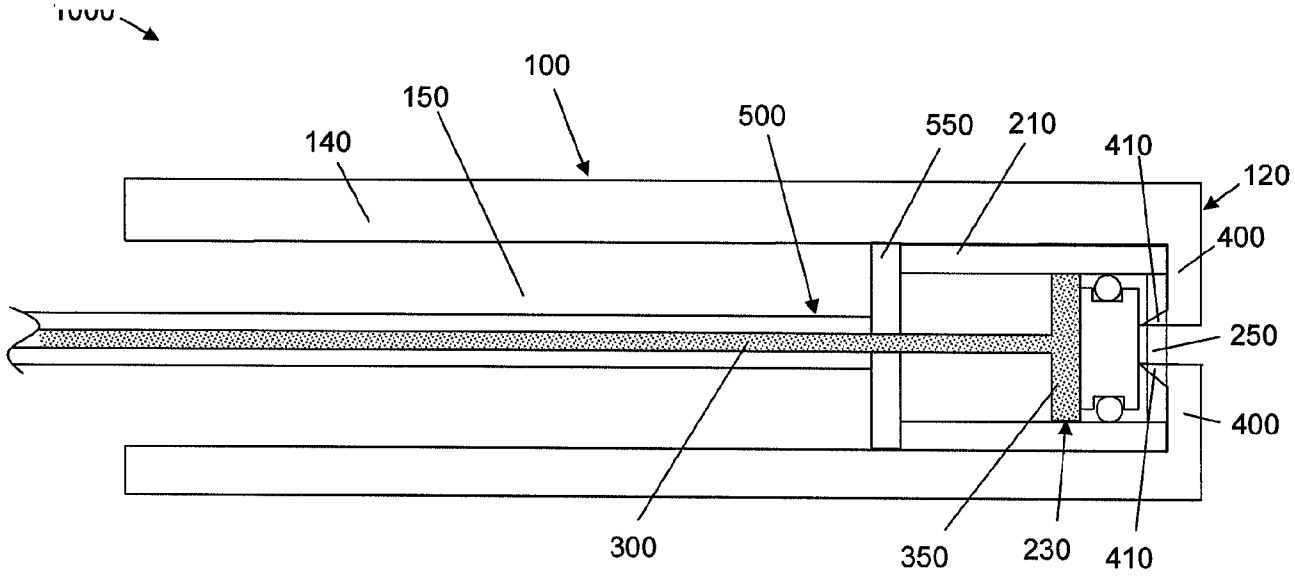

FIG. 9B

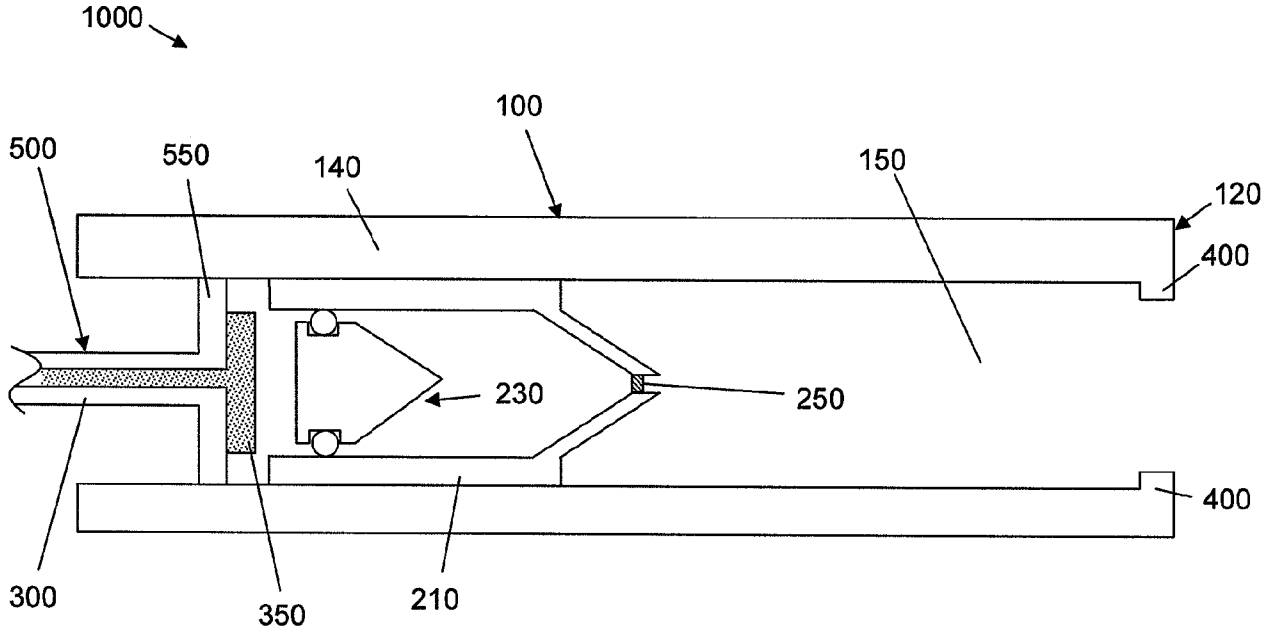

FIG. 10A

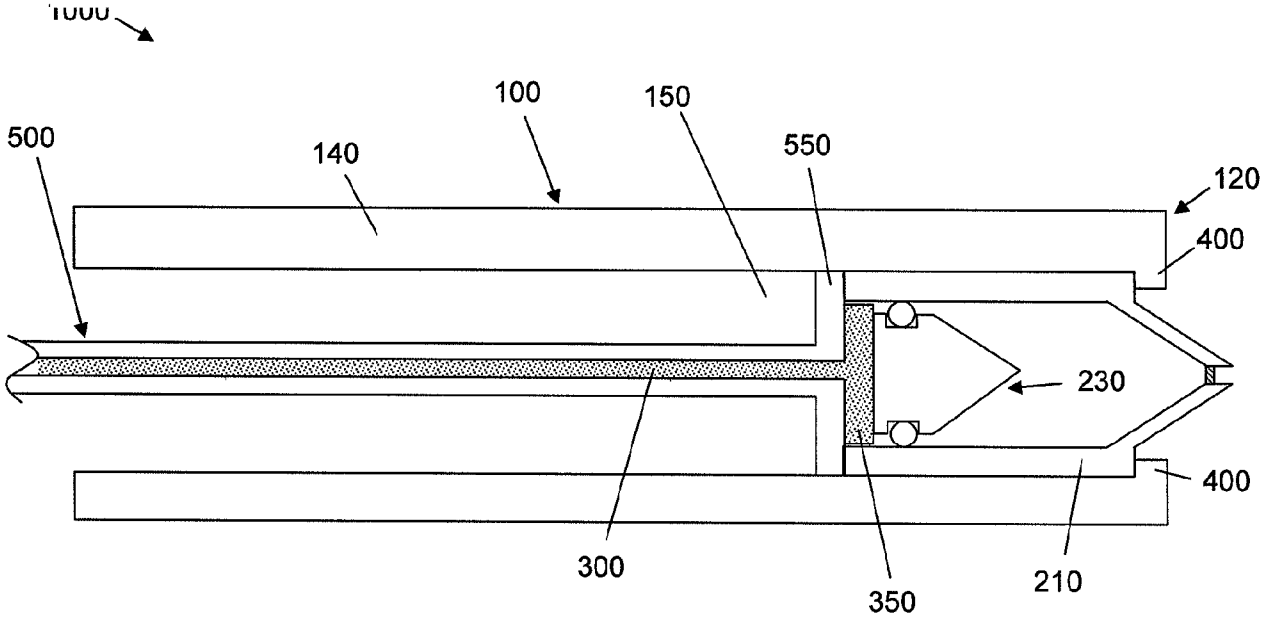

FIG. 10B

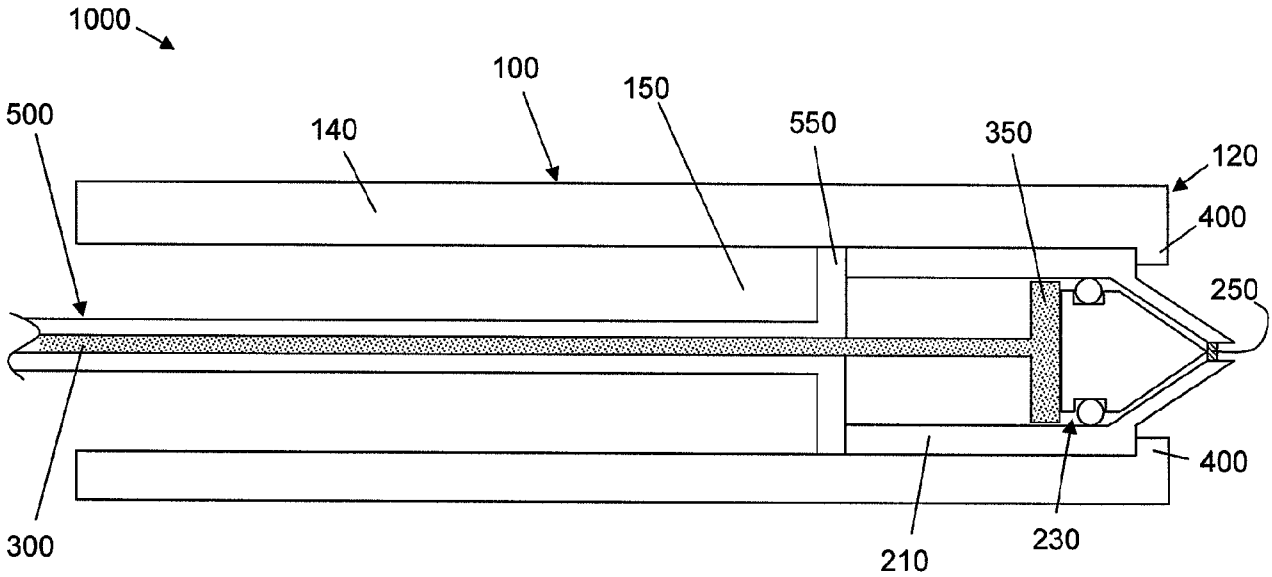

FIG. 10C

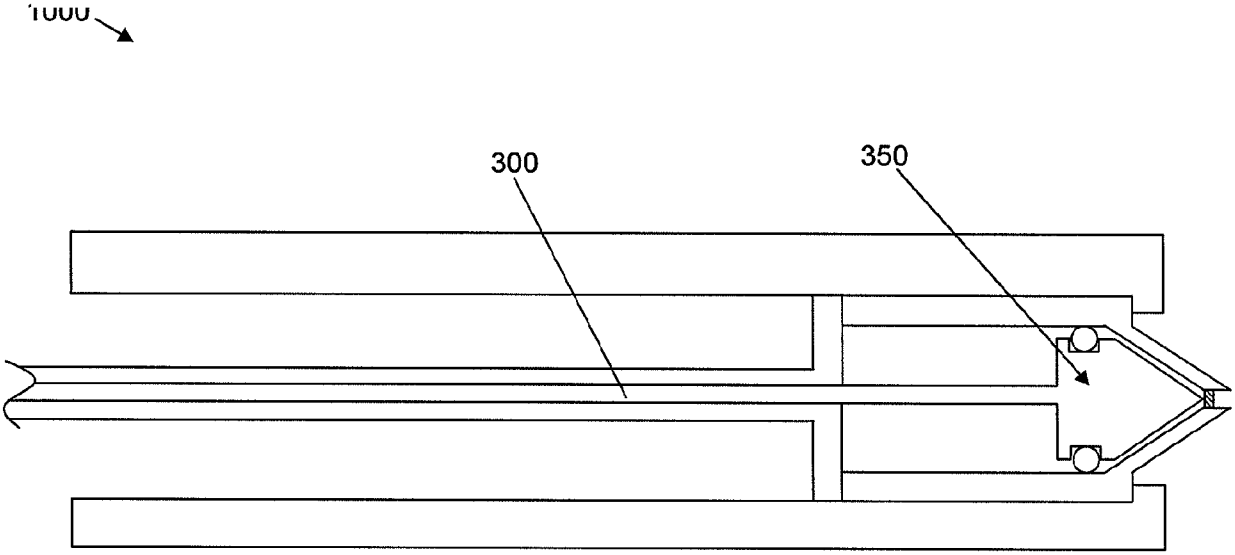

FIG. 11

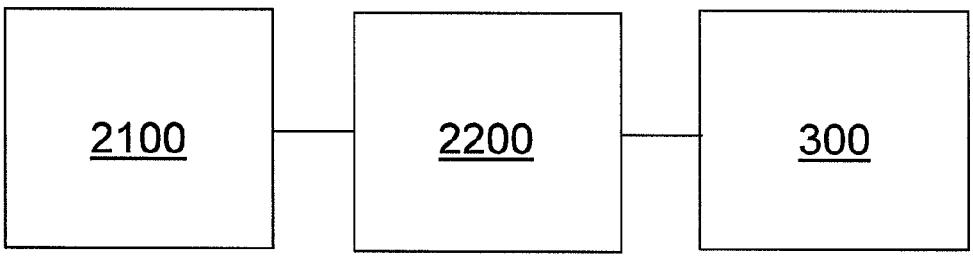

FIG. 12

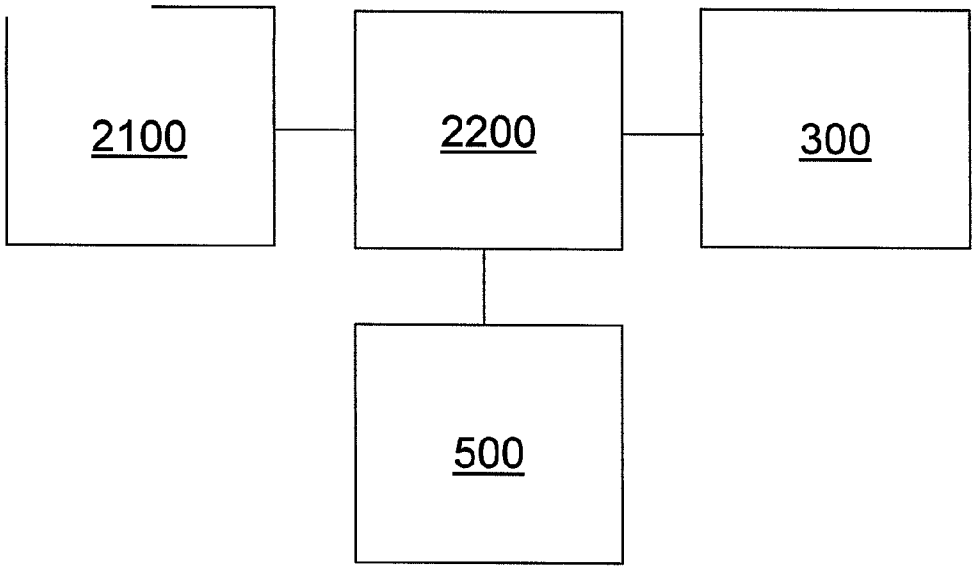

FIG. 13

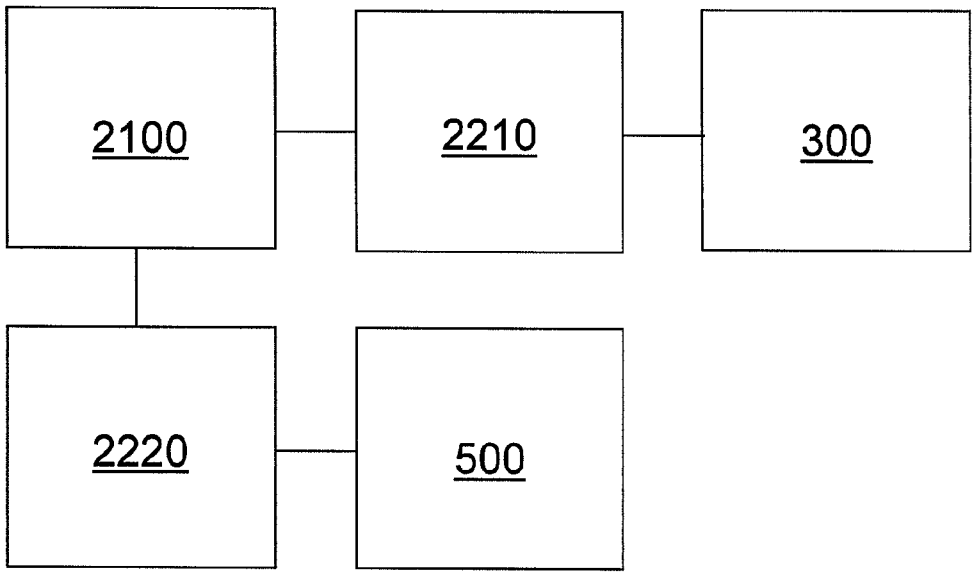

FIG. 14

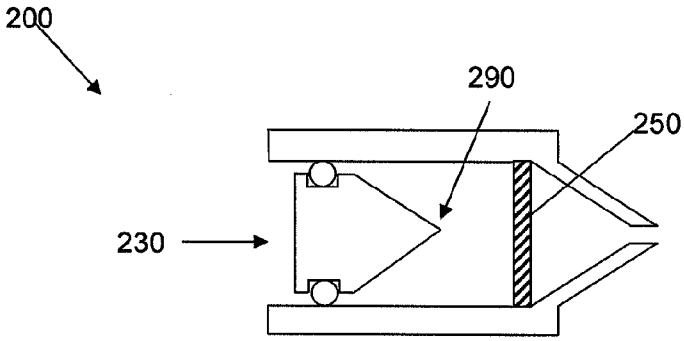

FIG. 15

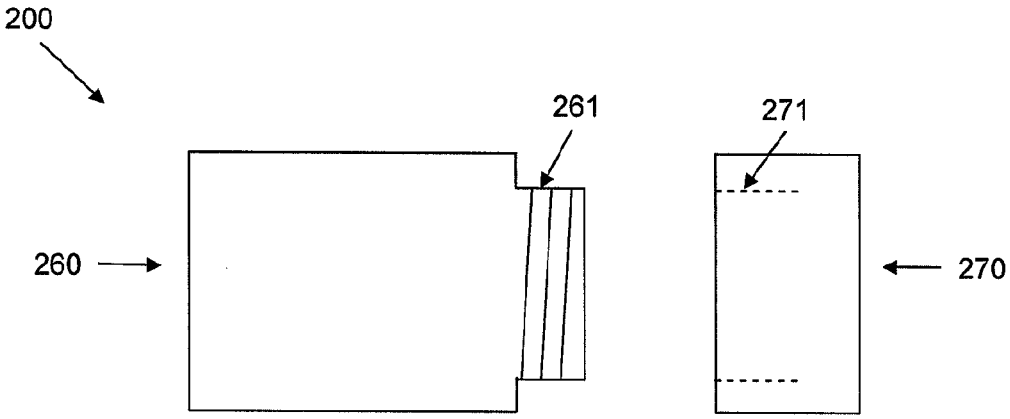

FIG. 16

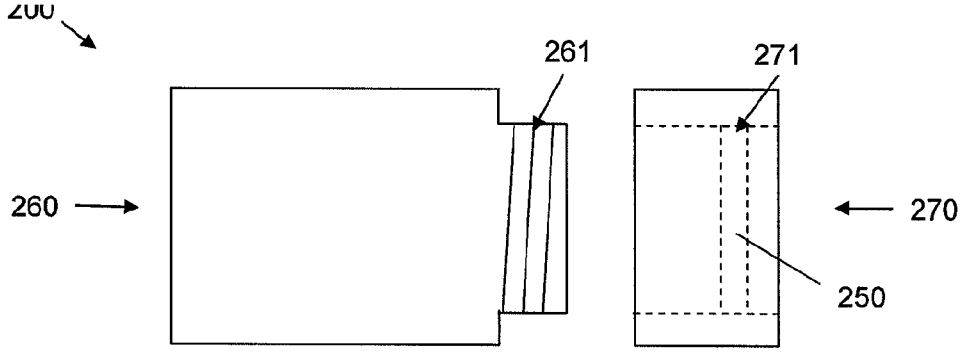

FIG. 17A

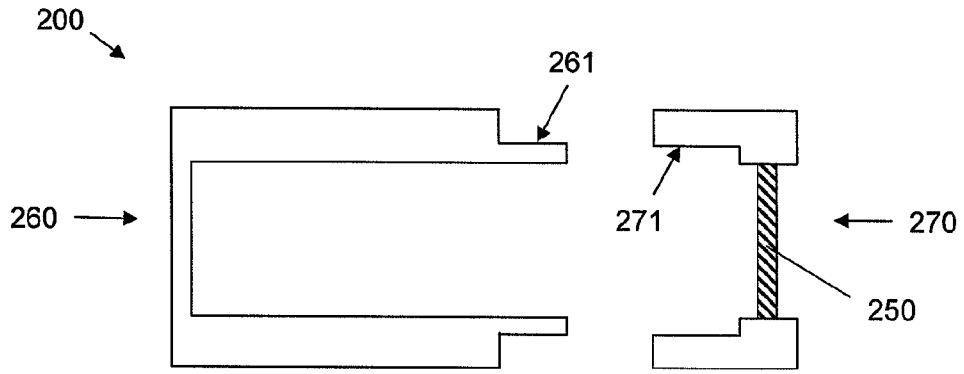

FIG. 17B

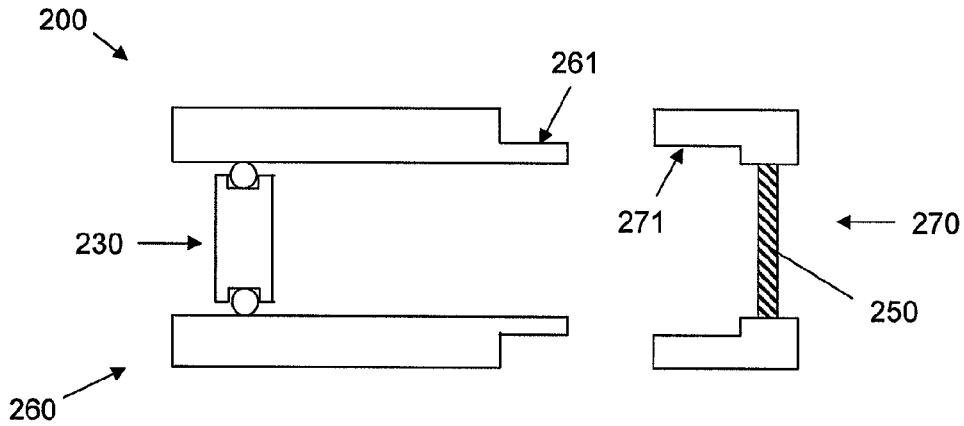

FIG. 18

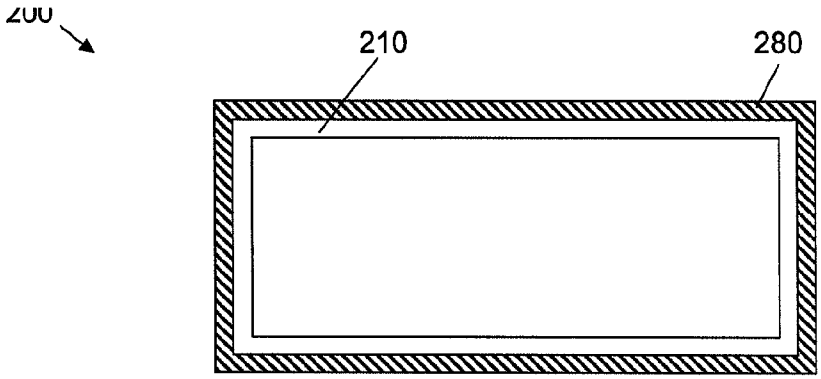

FIG. 19

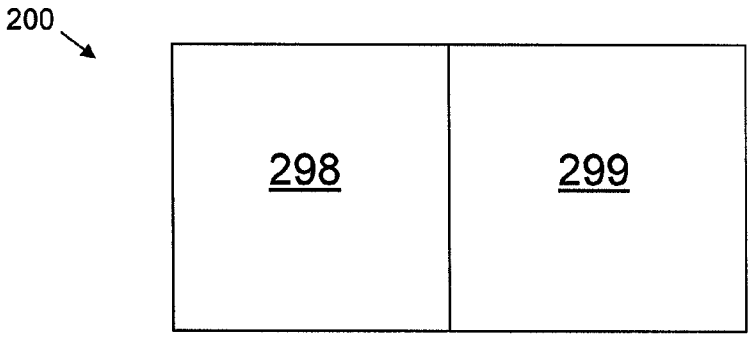

FIG. 20

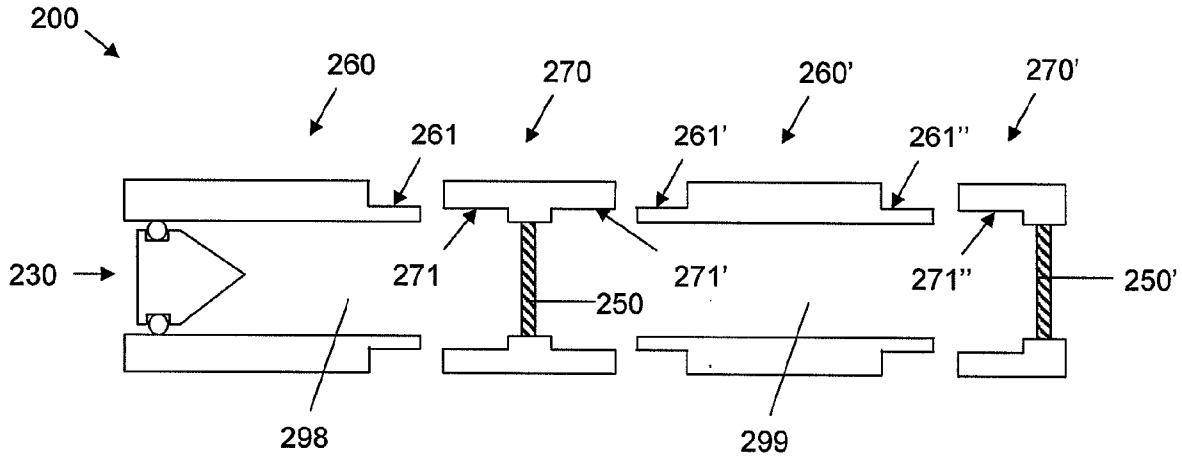
200
260
270
260'
270'
261
261'
261''
230
271
271'
271''
250
250'
298
299

FIG. 21

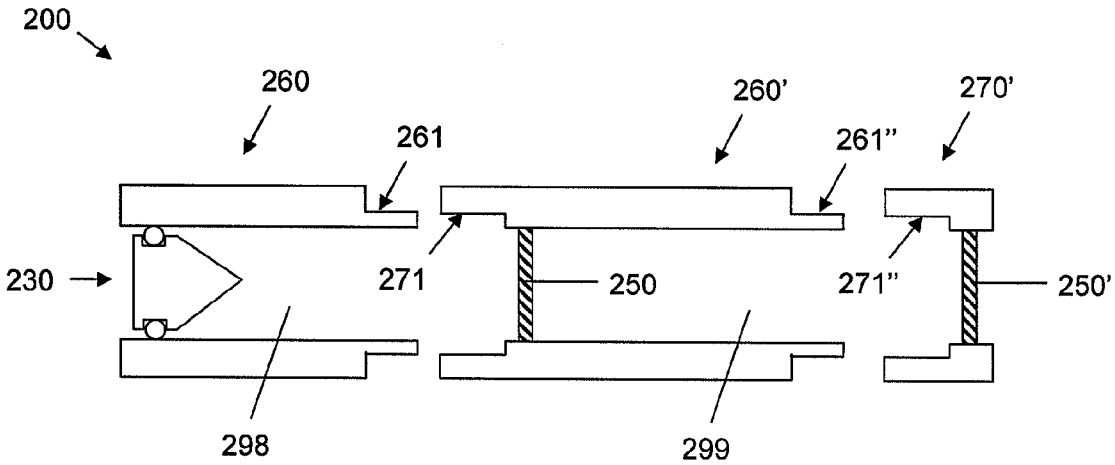
200
260
260'
270'
261
261''
230
271
250
271''
250'
298
299

FIG. 22

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/062725

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61M5/28 A61M25/00
ADD. A61M5/00

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)
A61M

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 practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2 778 360 A (MISKEL JOHN J) 22 January 1957 (1957-01-22) figures 1-6 column 2, line 47 - column 6, paragraph 57	1-20
X	WO 2005/072644 A1 (BIMEDA RES & DEV LTD [IE]; HALLAHAN STEPHEN [IE]; MCHARDY NICHOLAS [IE) 11 August 2005 (2005-08-11) figures 1-20 page 16, line 11 - page 22, line 4	1-20
X	WO 02/24248 A1 (KENSEY NASH CORP [US]; EVANS DOUGLAS G [US]; NASH JOHN E [US]; HOGANSO) 28 March 2002 (2002-03-28) figures 1-22 page 23, line 18 - page 34, line 4	1-4,6,8

-/--

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

[X] See patent family annex.

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"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

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"&" 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 February 2010	04/03/2010

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/062725

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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X	JP 05 300946 A (OLYMPUS OPTICAL CO) 16 November 1993 (1993-11-16) figure 26 paragraph [0086] -----	1-4,8
X,P	WO 2009/120960 A2 (ISCIENCE INTERVENTIONAL CORP [US]; YAMAMOTO RONALD [US]; CONSTON STANL) 1 October 2009 (2009-10-01) figures 1-3 paragraph [0014] - paragraph [0024] -----	1-4,6-7

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International application No
PCT/US2009/062725

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