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(71) Applicant: **CONNECTIVE ORTHOPAEDICS**  
[US/US]; 300 Trade Center, Suite 6650, Woburn, MA  
01801 (US).

(72) Inventors: **BANKS, Samuel, D., Jr.**; 119 Grant Street, #2, Lexington, MA 02420 (US). **BUSH, Katie, A.**; 9 Pratt Street, Apt. 2, Worcester, MA 01609 (US). **EGAN, Thomas, D.**; 12 South Street, Marblehead, MA 01945 (US). **FLEMING, Braden, C.**; 62 Limerock Drive, East Greenwich, RI 02818 (US). **MURRAY, Martha, M.**; 14 Peckham Hill Road, Sherborn, MA 01770 (US). **PALMER, Matthew**; 11 Farrell Drive, Brewster, NY 10509 (US). **SKINLO, David, M.**; 1316 East 1900 North, North Logan, UT 84341 (US). **WEISEL, Thomas, P.**; 3063 Grove Street, Ventura, CA 93003 (US). **WRIGHT, Emma**; 12 Pondview Road, #2, Arlington, MA 02474 (US).

(74) Agent: **POWERS, Elizabeth, E.**; Powers Law Firm, 1871 The Alameda, Suite 400, San Jose, CA 95126 (US).

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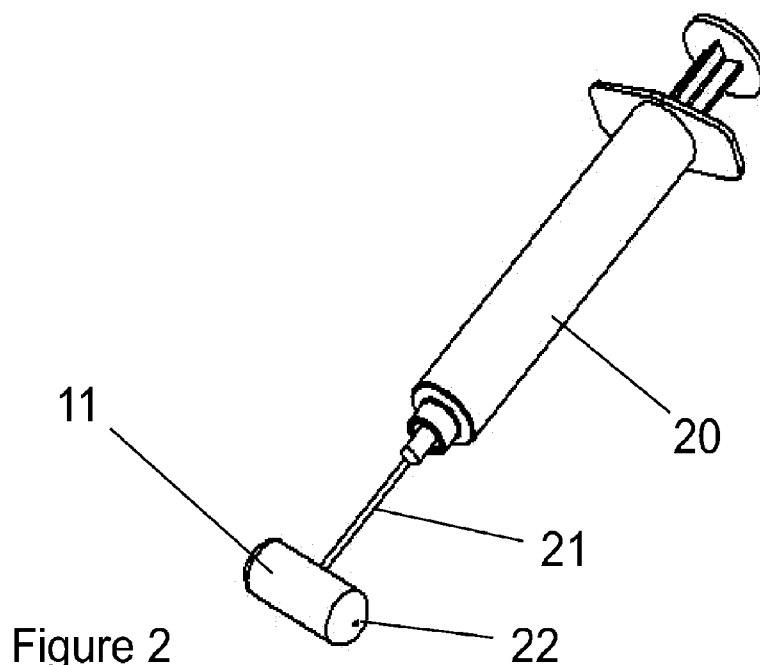


Figure 2

(57) Abstract: Devices and methods for activating a therapeutic composition, delivering a therapeutic composition to a specific region or tissue in a body, and containing a therapeutic composition within a body cavity are disclosed herein. In one embodiment, a therapeutic capsule is shown having an outer element defining an interior chamber and including a matrix disposed therein and wherein the interior chamber is elongated along a chamber axis.



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## ACTIVATION AND DELIVERY DEVICES FOR THERAPEUTIC COMPOSITIONS

**RELATED APPLICATIONS**

- [01] This application claims priority to the following U.S. Provisional patent applications: U.S. Serial No. 61/121,113, filed December 9, 2008; U.S. Serial No. 61/154,181, filed February 20, 2009; U.S. Serial No. 61/154,981, filed February 24, 2009; U.S. Serial No. 61/154,975, filed February 24, 2009; U.S. Serial No. 61/169,062, filed April 14, 2009; U.S. Serial No. 61/224,295, filed July 9, 2009; and U.S. Serial No. 61/228,657, filed July 27, 2009.

**FIELD**

- [02] The present invention relates to devices and methods for containing, preparing, delivering and maintaining the effects of a therapeutic composition for healing, repairing, or enhancing tissue in a body. The invention finds particular utility in preparing, delivering and maintaining therapeutic effects of a composition in body locations accessed by minimally invasive surgery (MIS) techniques. While embodiments of the present invention have application in providing therapeutic effects to a wide array of tissues in an animal body, applications are described herein involving healing, repairing and enhancing of connective tissues in the human musculoskeletal system for illustrative purposes. In particular, applications to soft tissues that are exposed to synovial fluid, such as the anterior cruciate ligament (ACL) of the knee and the rotator cuff tendons (RC) of the shoulder are described.

## BACKGROUND

[03] Most tissues in the body heal spontaneously when damaged. Other tissues, particularly intra-articular tissue, such as the anterior cruciate ligament (ACL) for example, fails to heal adequately after rupture, even after partial injuries or primary repair with sutures or other fixation devices. This phenomenon is quite different from the response of extra-articular injuries such as those to the medial collateral ligament (MCL) which often heals even with no surgical intervention. The lack of healing seen in the ACL and other intra-articular tissues has been attributed to the relative lack of vascularity of ACL's, the hostile environment of synovial fluid, alterations in the cellular metabolism after injury, intrinsic cell deficiencies, and the complex biomechanics of these tissues. However, recent publications have reported that human ACL remnants typically contain viable cells and vasculature, yet there is a gap at the rupture site which remains open. This gap is unique to the intra-articular environment of the ACL as it is not observed in repaired extra-articular ligaments.

[04] In a typical extra-articular MCL wound site, the gap resulting from rupture is filled with a provisional scaffold of fibrin and platelets that is subsequently invaded by surrounding intrinsic and extrinsic cells which initiate and conduct tissue healing. In the extra-articular environment the breakdown of this fibrin-platelet provisional scaffold occurs slowly over days to weeks in balance with new collagen formation at the injury site. In contrast, in the intra-articular environment of the ACL, such a stabilized fibrin-platelet clot is not observed to form even after induced bleeding into the joint. Thus, patients with an intra-articular injury form a hemarthrosis in the joint, without forming a stabilized fibrin-platelet scaffold at the wound site. The presence of urokinase

plasminogen activator found in the synovial fluid after injury may play a key role in this failure of a scaffold formation as the presence of this enzyme results in elevated levels of circulating plasmin in the joint and accelerated fibrin dissolution. Other intra-articular soft tissues in the body experience a similar resistance to healing to various degrees, including the meniscus and posterior collateral ligament (PCL) of the knee, the rotator cuff tendon and glenoid labrum in the shoulder, the labrum of the hip, and the triangular fibrocartilage complex (TFCC) of the wrist.

- [05] In addition to repair of native tissue, reconstruction of tissue in an animal by means of a graft is known to the art. Numerous examples of replacement or augmentation of weak or damaged ligament, tendon, cartilage, bone, muscle, vascular, nerve and organ tissues (hereafter “tissue”) with autograft, allograft, xenograft (hereafter “tissue graft”) or synthetic graft materials in the body have been demonstrated or hypothesized. All are potential beneficiaries of the present invention. Particular applicability can be seen in the use of tissue grafts to buttress, replace, or augment (hereafter “reconstruct”) ligament, tendon, cartilage, and fibrocartilagenous tissue (hereafter “connective tissue”) in the knee, shoulder, elbow, wrist, hip, ankle (“joints”) and spine. In practice, a reconstruction is rarely as strong as natural, healthy, uncompromised tissue. Animal studies show reconstruction grafts of the ACL, by example, typically restore only about 40% of pre-injury strength, putting the patient at risk of re-injury and early onset of degenerative joint disease. The graft initially has no blood supply and the original graft tissue degrades over time while at the same time it is being repopulated with new living cells which can remodel the graft and lay down new tissue. The need exists for materials and methods to

enhance and accelerate the cellular remodeling process, thereby improving graft characteristics such as strength, laxity and patient recovery time.

[06] To address this problem of non-healing soft tissues, certain therapeutic compositions have been developed to improve healing, integration, and remodeling of the newly implanted tissue graft. Recent studies have shown that new cellular growth in connective tissue can be brought about through the introduction of a composition of collagen, platelets, and at least one of an extracellular protein and a neutralizing agent, and subsequent related compounds. Other compounds include any combination of collagen (all types), proteoglycans, glycosaminoglycans, carbohydrates, synthetic material, (hereafter “matrix”) and one or more biologically active agents such as blood, plasma, platelet rich plasma, platelet poor plasma, bone marrow aspirate, stem cells, growth factors, proteins, peptides, etc. (hereafter “biologically active agents”), and in some cases inert ingredients such as gelling agents, foaming agents, gelatin, gelatin foam, cellulose, preservatives, textures, binders, etc. (hereafter “inert ingredients”). Collectively, these combinations of ingredients in any combination shall be referred to as “therapeutic compositions”.

[07] By applying these therapeutic compositions to damaged soft intra-articular tissue, one can create a provisional scaffold, a stabilized clot can be simulated that is subsequently invaded by surrounding intrinsic and extrinsic cells which initiate and conduct tissue regeneration. Breakdown of this fibrin-platelet provisional scaffold occurs slowly over days to weeks in balance with new collagen formation strengthening the repair.

[08] The physical configuration of the repair may take any of several forms. The repair may involve abutting or apposing two ends of torn tissue such as a ligament. In situations where the soft tissue to be repaired is load bearing, and immobilization of the patient is undesirable or impractical, a temporary fixation means, such as strands of suture, may be used to hold the soft tissue in apposition until healing can take place. Whether the soft tissue tear is within the middle portion of the soft tissue, or at the ends where it interfaces with other tissues (bone, muscle, etc.), the therapeutic composition can be placed around or throughout the defect to enhance healing in those regions. The repair may also involve bridging a gap of missing or severely compromised soft tissue where it is not possible to bring together the desired tissues. In these cases the therapeutic composition can be placed around the soft tissues and inside the gap between these tissues in order to allow cells to migrate into the gap between the two desired fixation points. Still other soft tissue injuries call for enhancement of stretched, partially torn or only weakened tissue. Additionally, therapeutic compositions may be used to improve biomechanical qualities of a tissue graft used to reconstruct native anatomy. It is therefore desirable to have a means to place a therapeutic composition against or around a tissue structure or to fill a gap in tissue or to fill a gap transited by suture or other repair structures.

[09] Amorphous therapeutic compositions that assume the shape of a body cavity into which they are delivered, are in contact with tissues enclosing the body cavity. Often the targeted tissue or injury is present in only a small region of the body cavity. When the therapeutic effects of the composition are delivered through contact, and only a small percentage of the tissues defining the body cavity are targeted for therapeutic effects, a large percentage of the therapeutic effects can be delivered to healthy tissue in no need of

healing. For example, a torn ACL of the knee could be treated by delivery of a therapeutic composition to the space surrounding the ACL (the intracondylar notch). An amorphous therapeutic composition could be injected into the intracondylar notch to surround and envelop the ACL, imparting therapeutic benefits through direct contact with the injured tissue. However, the composition would also be in direct contact with the posterior cruciate ligament (PCL), the cortical surface of the femur, the articular cartilage of the femoral condyles and tibial plateau, and the meniscus. It would be more efficient to deliver therapeutic composition only to the specific tissue to be treated. Thus, there is a need in some cases to contain the therapeutic composition in a region around a target tissue.

## SUMMARY

- [10] Devices and methods for activating a therapeutic composition, delivering a therapeutic composition to a specific region or tissue in a body, and containing a therapeutic composition within a body cavity are disclosed herein.
- [11] An embodiment of the device includes a hollow chamber containing a matrix, which may be an embodiment of a neutralized soluble extracellular matrix. In a preferred embodiment, the matrix is a dry porous sponge. In other embodiments, the matrix is a powder, solid, liquid, or gel. The device includes a means for adding a biologically active agent to the matrix to form a therapeutic composition. In a preferred embodiment, the biologically active agent is a liquid. In other embodiments, the biologically active agent is a powder, solid, liquid, or gel of a type capable of being mixed with the particular form

of the matrix. In an embodiment of the invention, the biologically active agent is whole blood, platelet-rich plasma (PRP), or saline.

- [12] In an embodiment, the chamber containing the matrix consists of a fully enclosed shell of biocompatible, bioabsorbable material, such as a gelatin capsule, sugar, cellulose, absorbable polymer, or similar material. The chamber is penetrated with a hypodermic type needle and injected with a quantity of a biologically active agent to activate the matrix and form a therapeutic composition. The chamber or capsule is placed in a part of the body, adjacent to the tissue to be treated and when the capsule dissolves or is absorbed, the therapeutic composition is released, treating the targeted tissue.
- [13] Alternatively the chamber or capsule may be placed in the body prior to activation and be activated by needle injection *in situ*. Other embodiments include a tube attached to the chamber communicating with the matrix, allowing delivery of a biologically active agent remotely. Still other embodiments are empty chambers with means for filling with therapeutic composition *in situ*. Some of these embodiments are collapsible to allow introduction to the body through a small opening, as in minimally invasive surgery (MIS). Other embodiments are not fully enclosed but have openings into which tissue to be treated may be placed.
- [14] In a preferred embodiment, the chamber and matrix take the form of a hollow sleeve with a therapeutic composition matrix attached to its inner surface that may be slid over a linear tissue structure, such as an ACL graft, such that the therapeutic composition is held in direct contact with the graft. In some embodiments, this sleeve is slid over the graft prior to placement in the body, or after one end of the graft is fixed in place. In other

embodiments the chamber and matrix is split such that it can be wrapped around the graft or linear tissue structure. Other embodiments of the implantable chamber include provision for sutures to be passed through the chamber to facilitate delivery to a targeted tissue or to fix the therapeutic composition in place in a body.

- [15] In another class of embodiments, the chamber containing the therapeutic composition is removed from the body after delivery of the therapeutic composition to the targeted tissue. The material of the chamber therefore need not be dissolvable or absorbable. This embodiment is particularly useful for therapeutic compositions that transition from a relatively amorphous state to a semi-solid state, and in environments like arthroscopic surgery where the saline fluid filled joint may fragment or dissolve the therapeutic composition when in its amorphous state. In this case the chamber provides a protective environment for delivery of the therapeutic composition and is removed when the material transitions to a gel-like state that is stable in the joint environment.
- [16] In other embodiments of the present invention, the chamber itself never enters the body, and only the therapeutic composition is delivered to the target tissue. In this class of embodiments, the chamber containing the matrix receives a biologically active agent through a passageway in communication with the matrix, and the activated therapeutic composition is ejected from the device into the body through a hollow delivery channel.
- [17] In an embodiment, the chamber is open at one end and a piston-like pusher ejects the activated therapeutic composition from the distal end of the device directly into a body opening. This and other embodiments may or may not have provisions for threading guiding/fixating sutures through the therapeutic composition mass.

- [18] In an embodiment, the chamber is substantially cylindrical with a proximal and a distal end, and the matrix is an elongated shape with an outside diameter, an inside diameter, and a length. In this embodiment, the passageway that delivers the biologically active agent is a tube that extends axially through the length of the chamber, through the inside diameter of the matrix, terminating near the distal end of the chamber. In this embodiment a piston moves the matrix axially toward the distal end while simultaneously another connected mechanism pumps a biologically active agent through the passageway toward the distal end of the chamber at a rate proportional to the movement of the matrix. In this way, the dry, sponge-like matrix is wetted from the inside with a progressively as it travels down the cylindrical chamber, and exits the cylindrical chamber as an activated therapeutic composition. The proportional relationship of the matrix advancing mechanism and the biologically active agent dispensing mechanism assure the proper ratios of each ingredient are maintained.
- [19] In an embodiment, the matrix is advanced as a single elongated piece, which preferably is a tube. In another embodiment, the matrix is comprised of a plurality of shorter tube segments. In another embodiment, the passageway introducing the biologically active agent does not extend axially through the center of the cylindrical chamber, but instead exists outside the lumen of the cylindrical chamber, communicating with the chamber near the distal end from the side wall of the chamber. In this embodiment, the matrix need not be tubular, but is instead cylindrical or otherwise conforming to the shape of the chamber. In another embodiment, the matrix segments of this type are loaded individually into the chamber from a magazine and advanced individually, while still maintaining the proportional relationship of matrix-to-biologically-active agent.

- [20] Mixing of the matrix and the biologically active agent to form the activated therapeutic composition may be accomplished in a variety of ways depending, on the nature of the matrix and agent. Where both are a liquid or gel, they may be mixed in the chamber using a stirring device, such as an impeller or screw auger. In an embodiment, the liquid or gel matrix and agent are mixed in a chamber using a helical screw auger that is axially compressible. A piston provides a means of propelling the activated therapeutic composition from the chamber, through a delivery channel and into a body. The helical auger compresses within the chamber allowing the piston to displace the volume therein.
- [21] In some embodiments, where the matrix is a dry, porous sponge and the biologically active agent is an aqueous liquid, the mixing process required for activation is facilitated by an inherent hydrophilic absorbency of the sponge; the matrix becomes fully saturated by coming into contact with the appropriate volume of a biologically active agent. In other embodiments, with less hydrophilic matrices, it is necessary to provide a means of inducing the two or more ingredients to thoroughly mix.
- [22] One means of inducing wetting is removal of air from the porous matrix, wetting in a vacuum, and then re-pressurizing to force the liquid into the pores of the sponge. In an embodiment, the chamber containing the dry matrix is evacuated of air and sealed, such that the matrix exists in a full or partial vacuum. A passageway for the introduction of a biologically active agent is provided but sealed until needed for activation (immediately prior to delivery to a body.) During activation, the biologically active agent is applied to the matrix in a vacuum and the chamber is re-pressurized by allowing atmospheric pressure air into the chamber, forcing the liquid agent onto the pores of the sponge matrix. In another embodiment, the chamber is re-pressurized by changing the volume of

the chamber to equalize pressure in the chamber with the surrounding atmosphere. In an embodiment, this is accomplished by providing a matrix in a cylindrical chamber with a piston. The piston is locked in a retracted position prior to evacuation of the chamber. A volume of a biologically active agent, calculated to fully saturate the matrix, is introduced into the chamber without allowing the admittance of air. At this point, the chamber contains partially wetted matrix sponge, liquid agent, and empty space in the form of sponge pores in a vacuum. Without allowing air into the chamber, the lock holding the piston in a retracted position is released and the piston is allowed to slide into the chamber, propelled by the pressure differential between the chamber (vacuum) and the surrounding atmosphere. As the piston slides into the chamber space, the evacuated pores are collapsed or filled with liquid agent until the piston stops moving and the pressure inside and outside the chamber is equalized. The resulting activated therapeutic composition has little or no entrapped air.

[23] An airless activated therapeutic composition has several advantages over activated therapeutic compositions with entrapped air: (i) it is roughly neutrally buoyant in the saline irrigated environment of arthroscopic surgery and will not float away; (ii) when extruded through a hollow delivery channel, it will not sputter and fragment like composition with air will; (iii) it is incompressible and will not compress and admit saline back flow when the delivery channel and chamber are exposed to pressurized arthroscopic saline; and (iv) it contains a higher concentration per unit volume of therapeutic agents than composition with entrapped air.

[24] In another embodiment, rather than evacuating and sealing the chamber at the time of manufacture, a means for evacuating the chamber at the time of use is provided. In this

embodiment, a vacuum source (a vacuum pump, an evacuated container, etc.) is connected to the matrix-containing chamber by a passageway equipped with a 3-way valve. In a first position, the valve connects the chamber to the atmosphere. In a second position, the valve connects the chamber to the vacuum source. In a third position, the valve connects the chamber to a reservoir containing a quantity of biologically active composition. By stepping through the valve positions, first, second, third, then back to first, the matrix has been vacuum activated. Alternatively, when a chamber with a locking piston is used, valve steps first, second, and third are followed by release of the piston lock, rather than switching the valve back to the first, vented, position.

[25] In some embodiments of the therapeutic composition, the matrix and biologically active agent are mixed at or near the time of their application to the repair site. This mixing process is referred to as “activation” of the therapeutic composition. In some instances, the matrix is a dry, absorbent substance like a sponge, and the biologically active agent is a liquid-based composition applied to the matrix immediately before, after, or during implantation to form the therapeutic composition. In some instances, the matrix is wetted with biologically active agent and assumes a flowable, amorphous state with a paste-like consistency where it is able to be delivered by injection or extrusion into a body using a device like a syringe.

[26] Once in the body, the amorphous material assumes the shape of the body cavity it is injected or extruded into. Some embodiments of the therapeutic composition transform in the body from an amorphous state to a non-flowable, semi-solid state, like a gel, foam, or solid. Other embodiments of the therapeutic composition retain their amorphous state after delivery. Some embodiments of the therapeutic composition that transition from an

amorphous, paste-like consistency to a semi-solid, gel-like consistency do so rapidly after activation by mixing matrix and active agent. In these embodiments, it is desirable to activate the composition immediately prior to delivery or even during the delivery process to prevent such composition transition prior to reaching the region of tissue to be healed.

- [27] Other embodiments include a dry, porous matrix, such as a collagen sponge, which is activated by mixing with a liquid biologically active agent, such as platelets, blood, or platelet-rich plasma (PRP), and where the resulting amorphous therapeutic composition is to be delivered to a target site by being pushed, injected, or extruded through a tube. In such instances, it is often desirable to remove air from the mixture to assure faster, more complete wetting, increase the density and concentration of the resulting composition, prevent back-flow of irrigation fluid due to compressibility of air-filled material, and prevent sputtering and fragmentation of the extruded material due to air entrapment.
- [28] An embodiment of the present invention includes a therapeutic capsule having at outer element defining an interior chamber and including a matrix disposed therein. In an embodiment, the interior chamber is elongated along a chamber axis, and the matrix includes a cylindrical central void region having a diameter  $D$  and extending from at least a first end thereof and along the chamber axis.
- [29] Another embodiment of the present invention includes a therapeutic kit, comprising a therapeutic capsule, having at outer element defining an interior chamber and including a matrix, such as a collagen matrix, disposed therein, together with an introducing device adapted to introduce a fluid biologically active agent to the matrix. In one embodiment, the introducing device of the kit includes a cylindrical elongated delivery element

disposed about a central void region extending along a delivery axis from a proximal end to a distal end thereof. The elongated delivery element further includes a cylindrical outer surface extending from the distal end along the delivery axis, and has a diameter less than or equal to D. In one embodiment, the central void region of the elongated delivery element is adapted at the proximal end to receive the fluid biologically active agent. The delivery element may include one or more radially extending holes near the distal end and extending between the outer surface and the central void region.

[30] In another embodiment of the therapeutic kit of the present invention, the introducing device is a syringe, having an elongated reservoir element disposed about a reservoir region and extending from a proximal end to a distal end along the delivery axis. In an embodiment, the introducing device further includes a piston, disposed in the reservoir element near the proximal end, and a cap at the distal end thereof, wherein the reservoir region is disposed between the piston and the cap, and wherein the cylindrical elongated delivery element extends from the cap, whereby the central void region is in fluid communication with the reservoir region.

[31] In another embodiment of the therapeutic capsule of the present invention, the outer element defines the chamber to be closed and fully enclosing the matrix. In an alternative embodiment, the outer element defines the chamber to be open-ended, having a first open end along the chamber axis at one end thereof, and a second open end along the chamber axis opposite thereto. The outer element may include a longitudinal slit therein, wherein the matrix is longitudinally segmented, and wherein each segment extends radially inward from the outer element and is tapered in a radial direction. In another embodiment, the outer element of the therapeutic capsule includes one or more through-holes extending radially therethrough.

- [32] In an embodiment of the invention, the outer element is longitudinally segmented into a plurality of segments extending in a direction substantially parallel to the chamber axis.
- [33] In an embodiment of the invention, the power element is longitudinally segmented into two segments, each of the segments having C-shaped cross-sections along the chamber axis.
- [34] In an embodiment of the therapeutic capsule of the present invention, the outer element is bioabsorbable. In alternative embodiments, the outer element is composed of one from the group consisting of gelatin, sugar, cellulose, and polymer. In yet other embodiments, the outer element includes an elongated extension extending therefrom, wherein the elongated extension defines an interior region in fluid contact with the chamber.
- [35] In an embodiment of the therapeutic capsule, the elongated extension is flexible. In another embodiment, the matrix is compressible and the outer element is flexible. In an alternative embodiment, the matrix is dry and porous. In an embodiment, the dry porous matrix is a sponge.
- [36] In an embodiment of the inventive therapeutic kit, the kit further comprises an introducing device adapted to introduce a fluid biologically active agent to the matrix. In an embodiment, the introducing device is a syringe. In an embodiment of the kit, the biologically active agent comprises platelet-rich plasma (PRP) or blood. In an embodiment of the inventive kit, the matrix is responsive to introduction of the PRP or blood to become amorphous. In alternative embodiments, the biologically active agent may be PPP, whole blood, or platelets.
- [37] One embodiment of an activation device for a therapeutic compound of the present invention, an outer element defines an interior chamber and includes a dry porous matrix,

such as a collagen matrix, disposed therein, wherein the outer element defines the chamber to be closed and fully enclosing the matrix, wherein the chamber is characterized by a static pressure above or below ambient, and wherein the outer element is adapted to receive a delivery element for infusing said matrix with a biologically active agent.

[38] In an alternative embodiment of the inventive therapeutic kit for a therapeutic compound, the kit further includes an activation device, and an introducing device adapted to introduce a fluid biologically active agent through the outer element and into the matrix.

[39] In an embodiment of an activation device for a therapeutic compound, the device further comprises an outer element defining a cylindrical interior chamber extending along a central axis, the chamber having a piston disposed at one end thereof, and being sealed at the other end thereof. In that embodiment, the chamber includes a dry porous matrix, such as a collagen matrix, disposed therein, further including a selectively operative latch assembly, operative in a first state to fixedly hold, or lock the piston in the chamber, and operable in a second state to release the plunger allowing motion of the plunger in the chamber along the central axis in response to a pressure differential across the plunger, and wherein the chamber is characterized by a static pressure below ambient, and wherein the piston is adapted to receive a delivery element for infusing the chamber with a biologically active agent.

[40] In an embodiment of an inventive introducer for allowing passage of a compressible cylindrical therapeutic capsule disposed on an axial extending suture, the introducer comprises a tube extending along an introducer axis from a proximal end to a distal end, wherein the tube is characterized by a monotonically increasing diameter from the

proximal end to the distal end, and wherein the tube included a longitudinal slit extending from the proximal end to the distal end.

- [41] In an embodiment of an inventive delivery kit for delivering a therapeutic compound, the compound including a cylindrical, suture-bearing, dry porous matrix, such as a collagen matrix, the kit includes: (i) an outer elongated element having a length  $L_1$  and extending from a proximal end to a distal end along a delivery axis and defining an inner cylindrical region; (ii) an inner elongated element having a length  $L_2$ , where  $L_2$  is greater than  $L_1$ , and disposed slidably within the inner cylindrical region of the outer elongated element, and extending from a proximal end to a distal end along the delivery axis, and defining an inner cylindrical region having diameter  $D_1$ ; (iii) a pusher assembly extending along a pusher axis from a matrix pusher element at a proximal end to a control pusher element at a distal end, wherein at least the matrix pusher element at the distal end is adapted to slide within the inner cylindrical region of the inner elongated element with the pusher axis being substantially coaxial with the delivery axis. In an embodiment of the inventive kit, the matrix pusher element extends transverse to the pusher axis and the pusher element has a circumferential edge has a diameter slightly less than  $D_1$  and includes a plurality of void regions extending radially inward from the circumferential edge. In an embodiment of the inventive kit, the control pusher element is rigidly coupled to the matrix pusher element by an intermediate element, and a plurality of elongated suture capture devices, each suture capture device extending along a suture device axis from a handle portion at a proximal end to a suture capture portion at a distal end, and having a length greater than  $L_2$ .

- [42] In an embodiment of a therapeutic composition containment device of the present invention, the device comprises an elongated primary shaft, extending from a proximal end to a distal end along a shaft axis, defining a primary interior region extending along the shaft axis from the proximal end to the distal end. The embodiment further comprises a containment structure extending from the distal end of the elongated shaft, and having two states: (i) a first state, wherein the containment structure is C-shaped and disposed about a central axis transverse to said shaft axis, and extends between opposite ends thereof and defining a gap between said opposite ends; and (ii) a second state, wherein the containment structure is ring-shaped and disposed about the central axis, the ring-shaped containment structure having an innermost surface defining an open faced circular channel extending circumferentially about the central axis, the channel being in fluid communication with the interior region of the shaft.
- [43] In an embodiment of a containment device of the present invention, a central axis intersects with and is perpendicular to the shaft axis. In an alternative embodiment, the inventive device includes a state control assembly selectively operable from the proximal end to control the containment structure to be in the first state with the gap being substantially closed, and in the second state with the gap being opened and having a predetermined non-zero value.
- [44] In an embodiment of a containment device of the present invention, the device further comprises an outer elongated shaft, disposed along an outer axis and defining an interior region extending along the outer axis, with the outer elongated shaft being adapted to overfit the primary elongated shaft with the outer axis substantially parallel with the shaft axis, whereby the primary elongated shaft can slide within the outer elongated shaft, and

wherein the containment structure is compressible to permit positioning within the interior region of the outer elongated shaft.

- [45] In an embodiment of an apparatus for loading a therapeutic composition, where the therapeutic composition includes a matrix and a biologically active agent (BAA), the apparatus comprises: (i) a delivery device, defining an interior cylindrical mixing chamber extending along a central axis between a proximal end and a distal end, and including at the distal end, a delivery tube extending therefrom along the central axis from the distal end to a delivery tip, the delivery tube defining an interior region extending along said central axis and having length  $L$  and a minimum dimension  $D$  transverse to said central axis and being in fluid communication with said Interior mixing chamber; (ii) an activation assembly including a housing having a vacuum port, a biologically active agent (BAA) port, and a loading port and a valve, wherein the vacuum port, the BAA port, and the loading port are coupled to the valve, wherein the valve is operative in a first state, to couple the vacuum port to the loading port, and in a second state, to couple the BAA port to the loading port; and (iii) an elongated mixing tube, coupled to and extending from the loading port, wherein the mixing tube defines an interior BAA flow region extending along a BAA loading axis between the loading port and a distal end of the mixing tube.

- [46] In an alternative embodiment of the inventive apparatus, the length of the BAA flow region is greater than  $L$ , and the mixing tube includes a plurality of radially-extending holes disposed near the distal end of the mixing tube, with the holes coupling the BAA flow region to points outside the mixing tube, wherein the maximum diameter of the mixing tube is less than  $D$ . In an alternative embodiment, a vacuum supply is coupled to

the vacuum port. In an alternative embodiment, a BAA reservoir is coupled to the BAA port. In yet another embodiment of the inventive apparatus, a piston is disposed in the cylindrical mixing chamber together with an associated driver, the piston being adapted for motion along the central axis in response to user-controlled action on the driver. In yet another embodiment, the loading port includes a seal for receiving the delivery tip, whereby the interior region of the delivery tube is in fluid communication with the loading port, with the mixing tube disposed within the delivery tube, and with the central axis being substantially coaxial with the BAA loading axis.

- [47] In an embodiment of an apparatus of the present invention for loading a therapeutic composition, the therapeutic composition includes a matrix and a biologically active agent (BAA), to a delivery device, whereby the matrix and the BAA are intermixed.
- [48] In an embodiment of an activation and dispensing kit for a therapeutic compound, the kit comprises: (i) a biologically active agent (BAA) container defining an interior BAA region extending from a closed proximal end to an elongated, cylindrical open distal end having a diameter R disposed about a BAA axis, and includes a BAA coupler at the open distal end; and (ii) an activator/dispenser. In an embodiment, the activator/dispense includes: a housing; an elongated dispensing tube defining an elongated cylindrical dispensing region extending from the housing to an open distal end along a dispensing axis A; an elongated hollow needle extending from the housing, and defining an interior needle region extending from a proximal end within the housing to a closed distal end within the dispensing tube, wherein the dispensing tube and the hollow needle are coaxial along axis A and define an annular matrix reservoir region in the dispensing region between the dispensing tube and the needle, and wherein the needle includes at or near its

distal end, one or more holes coupling the interior needle region with the matrix reservoir region; an elongated matrix pusher having an annular proximal end having an outer diameter greater than R and an extended elongated distal end extending therefrom coaxial along axis A, wherein the distal end is disposed in the matrix reservoir region; a central bore disposed in the matrix reservoir region and extending from an annular proximal end having an outer diameter greater than R; a BAA coupling assembly affixed to the proximal end of the needle, including an annular resilient seal having diameter R and disposed about the proximal end the interior needle region, the BAA coupling assembly being adapted to receive the BAA container, whereby the BAA axis is coaxial with the dispensing axis A and the interior BAA region is fluidly coupled to the interior needle region; and, an actuator assembly, including means for advancing a BAA container coupled to the BAA coupling assembly about the seal, whereby the open end of the BAA container is translated in the direction of the dispensing axis A.

- [49] In an alternative embodiment of the inventive kit, the advancing means of the actuator assembly is selectively operative in a first state to advance a BAA container toward the distal end of the dispensing tube and in a second state to advance a BAA container away from the distal end of the dispensing tube. In yet another embodiment of the inventive kit, the advancing means is a selectively bidirectional ratcheting assembly. In yet another alternative embodiment of inventive kit, the one or more holes coupling the interior needle region with the matrix reservoir region, are a plurality of radially extending holes extending from points near the distal end.

#### **BRIEF DESCRIPTION OF THE DRAWINGS**

- [50] Figure 1a is an isometric view of an embodiment of the invention.

- [51] Figure 1b is a partial cutaway isometric view an embodiment of the invention.
- [52] Figure 2 is an isometric view of an embodiment of the invention.
- [53] Figure 3 is an isometric view of an embodiment of the invention.
- [54] Figure 4A is an isometric view of an embodiment of the invention.
- [55] Figure 4B is a cutaway isometric view of an embodiment of the invention.
- [56] Figure 5a, 5b, and 5c are isometric views of an embodiment of the invention.
- [57] Figure 6a is an isometric view of an embodiment of the invention.
- [58] Figure 6b is a detail partial cutaway isometric view of the embodiment of the invention shown in Figure 6a.
- [59] Figure 7 is a partial cutaway isometric view of an embodiment of the invention.
- [60] Figure 8 is a partial cutaway isometric view of an embodiment of the invention.
- [61] Figure 9a is an exploded isometric view of an embodiment of the invention.
- [62] Figure 9b is a half-section isometric view of an embodiment of the invention.
- [63] Figure 10a is an exploded isometric view of an embodiment of the invention.
- [64] Figure 10b is an isometric view of the embodiment of the invention shown in Figure 10a.
- [65] Figure 11a includes both a plan view and a longitudinal half-section view of an embodiment of the invention.

- [66] Figure 11b includes both a plan view and a longitudinal half-section view of an embodiment of the invention.
- [67] Figure 11c includes both a plan view and a longitudinal half-section view of an embodiment of the invention.
- [68] Figure 12 is an isometric view of a prior art bone-tendon-bone autograft.
- [69] Figure 13a is an exploded isometric view of an embodiment of the invention.
- [70] Figure 13b is an isometric view of the embodiment of the invention of Figure 13a.
- [71] Figure 14 is an isometric view of an embodiment of the invention.
- [72] Figure 15a is an isometric view of an embodiment of the invention.
- [73] Figure 15b is a detail cross-section view of the embodiment of the invention shown in Figure 15a.
- [74] Figure 16 is an isometric view of an embodiment of the invention.
- [75] Figure 17a is an isometric view of an embodiment of the invention.
- [76] Figure 17b is a detail isometric view of the embodiment of the invention shown in Figure 17a.
- [77] Figure 18 is an isometric view of a prior art arthroscope.
- [78] Figure 19 is an isometric view of an embodiment of the invention.

- [79] Figure 20a is a detail isometric view of a containment chamber of the invention shown in Figure 19, in an open position.
- [80] Figure 20b is a detail isometric view of the containment chamber shown in Figure 19, in a closed position.
- [81] Figure 21a is a detail isometric view of a containment chamber of the invention, in a closed position.
- [82] Figure 21b is a detail isometric view of the containment chamber shown in Figure 21a, in an open position.
- [83] Figure 22 is an isometric view of an embodiment of the invention.
- [84] Figure 23a is a side plan view of an embodiment of the invention, with the cover removed, and with the trigger lever in a first position.
- [85] Figure 23b is a plan view of the embodiment of the invention shown in Figure 23a, with the trigger lever in a second position.
- [86] Figure 24 is a side plan view of an embodiment of the invention, with covering removed.
- [87] Figure 25a is an isometric view of an embodiment of the invention with the side covering removed.
- [88] Figure 25b is a detail, partial cutaway section, isometric view of a shaft chamber of the invention.
- [89] Figure 25c is a detail, partial section, isometric view of a shaft chamber of the invention.

- [90] Figure 26a is a detail schematic cross-section of an integral PRP extraction system of the invention.
- [91] Figure 26b is a detail schematic cross-section of one aspect of the integral PRP extraction system of Figure 26a.
- [92] Figure 26c is a detail schematic cross-section of one aspect of the integral PRP extraction system of Figure 26a.
- [93] Figure 27a is a side plan view of a therapeutic compound dispensing element of the invention.
- [94] Figure 27b is a hidden line plan view of the therapeutic compound dispensing element shown in Figure 27a.
- [95] Figure 28a is a side plan view of an embodiment of the invention.
- [96] Figure 28b is a hidden line side plan view of the embodiment of the invention shown in Figure 28a.
- [97] Figure 29 is an isometric hidden line perspective view of an embodiment of the invention.
- [98] Figure 30a is a schematic of a valve the invention, in a storage position.
- [99] Figure 30b is a schematic of a valve of the invention, in a first position.
- [100] Figure 30c is a schematic of valve of the invention, in a second position.
- [101] Figure 31 is an isometric view of a component of an embodiment of the invention.

- [102] Figure 32 is a longitudinal cross-section view of a chamber of the invention.
- [103] Figure 33 is a longitudinal cross-section view of a chamber of the invention.
- [104] Figure 34a is a longitudinal cross-section view of a chamber of the invention.
- [105] Figure 34b is a longitudinal cross-section view of a chamber of the invention, showing the end cap removed.
- [106] Figure 35 is an isometric view of an embodiment of the invention.
- [107] Figure 36 is an isometric view of an embodiment of the invention.
- [108] Figure 37 is an isometric view of an activated form of the invention shown in Figure 36.

### DETAILED DESCRIPTION

- [109] Figure 1a shows an embodiment of the present invention device **10**. Figure 1b shows a one quarter cutaway view of the embodiment of Figure 1a showing a chamber **11** containing a matrix **12**. In an embodiment the chamber **11** is gelatin. In an embodiment the matrix **12** is a collagen sponge, and preferably may be a soluble type I collagen.
- [110] Figure 2 shows a biologically active agent (BAA) in a syringe **20** being delivered to the matrix in the chamber **11** through a passageway **21** (in this illustrated embodiment, a hypodermic type needle) to form an activated therapeutic composition. In this illustrated embodiment, a small vent hole **22** vents any air or gas in the matrix displaced by the introduction of the biologically active agent. In an embodiment, the biologically active

agent is platelet rich plasma (PRP). In alternative embodiments, the agent may be whole blood, saline, or PPP. In this embodiment, the device **10** is then placed in a body adjacent tissue targeted for treatment. When the gelatin chamber dissolves, the activated therapeutic composition comes in contact with the target tissue and provides a therapeutic benefit.

[111] Figure 3 shows another embodiment of the inventive device **30** comprising a chamber containing a matrix that has been formed in a shape to provide tissue repair to a specific tissue in a specific anatomic region of a body. The illustrated device **30** is designed for use in repairing an ACL located in the femoral condylar notch of the right human knee. In this embodiment, the device **30** is pliable and so the shape need only be approximate. The overall tombstone shape is designed to conform to the condylar notch. A wide diagonal slot **31** conforms to the intact posterior collateral ligament (PCL) and a narrower slot **32** envelops a suture or other structural filament installed to stabilize the joint during the healing process. In one embodiment, the entire surface of the device is covered by the chamber. In another embodiment, the portion of the chamber corresponding to the insertion sites, or attachment points of the repaired ACL, have been removed to directly expose the therapeutic composition to the surfaces to which the repaired ACL will establish in-growth.

[112] Figure 4A shows two states of another embodiment of the present invention device **40** designed to be delivered to the tissue repair site through a small incision or anatomic passageway. In its collapsed state **41** the device comprises a chamber containing a compressed matrix, pleated and folded into a small diameter, substantially cylindrical

shape. Once placed in a body at the tissue repair site, the matrix is activated by the introduction of biologically active agent, thus expanding it into a larger volume state **42**.

In another embodiment, the pleated chamber is empty when placed in the body and is expanded with a therapeutic composition *in situ* activated elsewhere outside the body, and delivered through a passageway communicating with the chamber.

[113] Figure 4B is a cross-section view of two states, compressed state **41** and expanded state **42**, of the same device **40**, showing the pleats and folds **43** in the collapsed state **41**, and the interior volume filled with activated therapeutic composition **44**.

[114] Figure 5a shows an embodiment of the present invention device **50** that is designed to be delivered through a small opening in a body. In this embodiment, a flexible chamber houses a matrix that is elastically resilient, and springs back to roughly its original shape when de-compressed. A compression element **51** is included with a larger, first end opening **52** transitioning to a smaller second end opening **53**. The smaller, second end opening **53** is placed in an opening in a body through which the device **50** is to be delivered. The compression element **51** may be equipped with a flange **54** to control its depth of insertion into the body opening, and a slot **55** to allow a continuous loop of suture passing through the device **50** to be removed through the side of the compression element **51**.

[115] Figure 5b shows the embodiment device **50**, after having been pushed into the larger first end opening **52** of compression element **51** in the direction of arrow **56**, emerging from smaller, second end **53**, as it would appear emerging into a body.

[116] Figure 5c shows device **50** having exited the smaller, second end opening **53** of compression element **51**. Compression of the device **50** allows it to be implanted through an incision or body opening smaller than its own diameter. The elastic resiliency of the matrix contained within a flexible chamber allows the device to resume its shape inside the body. In an embodiment, the matrix contained within the chamber is activated by injection of BAA *in situ*.

[117] Figure 6a and detail Figure 6b show, in partial section view, an embodiment of the present invention device **60**, having an outer element **11** defining an interior chamber filled with matrix **12**, elongated along a chamber axis **CA**, and which interior chamber includes a cylindrical central void region **12a**, shown in Figure 6b as being filled with the removable passageway **62**. As illustrated, the interior chamber **12** is shown with a matrix material therewithin. The device **60** includes a central opening **61** into which has been inserted a removable passageway **62** with a first end **63** running through the central opening **61** of the device **60** with a series of radial holes **64** distributed along the portion of its length running through the device **60**, and second end **65** in fluid communication with a syringe **66** for injecting biologically active agent. Once activated, the fill tube **62** is removed.

[118] Figure 7 shows an embodiment of the present invention device **60** including a suture snare **70** with a first end formed in a loop **71** and a second end having a tab **72** to facilitate grasping with fingers. In practice, suture is threaded through the loop **71** and the user grasps the tab **72** and pulls suture through the central opening **61**.

- [119] Figure 8 shows an embodiment of the present invention device **60** where a suture **80** has been pulled through the central opening **61** shared with removable passageway **62**. In an embodiment, suture **80** is used to guide device **60** into place in a body, or to secure it to tissue, or both.
- [120] Figure 9a shows an exploded view of another embodiment of the present invention. This embodiment comprises a matrix **91**, one or more suture snares **92** inserted through the matrix, a passageway **93**, a chamber **94** equipped with a split flexible opening **98**, and a pusher **95**.
- [121] Figure 9b shows an isometric section view of the same device as shown in Figure 9a, assembled for use. In use, guide or fixation sutures are pulled through the matrix using the suture snares. Biologically active agent is introduced into the proximal opening **96** of the passageway **93** (in an embodiment held vertically and dribbled in via gravity or, in another embodiment, injected from a syringe) where it activates the matrix to form an activated therapeutic composition. The entire assembly is slid along the guide/fixation sutures (not shown) into an opening in a body. Pusher **95**, having slots to provide clearance for sutures, is introduced through the proximal end of the passageway **96** and pushes the activated therapeutic composition out of the distal end **97** of the chamber **94** that is equipped with a split flexible opening **98** to minimize backflow of body or irrigation fluids, yet allow the emergence of the therapeutic composition in the body.

[122] Figure 10a shows an isometric exploded view of another embodiment of the present invention comprising a matrix **100** with a central opening **101**, a chamber **102**, a fenestrated passageway **103**, and a means of propelling a quantity of biologically active agent through the passageway into the matrix in the chamber consisting of a cylindrical body **104** and a piston **105**. Figure 10b shows the same embodiment of Figure 10a, in its assembled state.

[123] Figure 11a shows this same device in plan view and section view as it would appear when ready for use. Chamber **102** contains a matrix **100**. Cylindrical body **104** contains a quantity of biologically active agent (BAA) **110**. Piston **105** and cylindrical body **104** translate linearly within chamber **102** and are both in a relatively retracted position.

[124] Figure 11b shows piston **105** translated to the right, displacing biologically active agent through fenestrated passageway **103** and into matrix **100**, thereby forming an activated therapeutic composition.

[125] Figure 11c, shows the device the distal end **111** of the chamber **102**, has been placed in a body (not shown). Cylindrical body **104** is translated to the right, ejecting matrix **100**, which has now become an activated therapeutic composition, into the body adjacent a tissue to be treated.

[126] Figure 12 shows a bone-tendon-bone autograft **121** typical of the type used in best practice ACL reconstruction surgery at the time of this writing. The graft comprises a proximal end **122** of bone harvested from the patient's patella, a graft midsection tendon

portion **123** harvested from the patient's patellar ligament, and a distal end **124** of bone harvested from the patient's tibia. The proximal and distal end boney plugs have been trimmed to pass freely through an 8mm bone tunnel. Although a bone-tendon-bone autograft will be used throughout this description the same invention application applies to all types of tissue grafts, including but not limited to soft tissue (e.g. hamstring) autografts, and all types of allografts and xenografts used for connective tissue reconstruction.

[127] Figure 13a shows a preferred embodiment for applying a therapeutic composition to a graft extra-corporeally, prior to implantation. This example shows two halves of a split tube **130** and **131** of matrix material. Other embodiments employ a tubular matrix with one split side that can be spread open to wrap around the graft. Still other embodiments use a graft split into three or more segments that are placed around the graft. In an embodiment the matrix is a sponge of collagen, such as Type I collagen. Figure 13b shows the saturated collagen tube halves placed around the tendon portion of the graft and held in place by a chamber **132**. Once so assembled, biologically active agent is applied to the exposed end of the matrix where it wicks along the entire length of the matrix. To accelerate the wicking process, a passageway like a small tube may be inserted into the space in the chamber occupied by the matrix and biologically active agent may be forced in to facilitate wetting and activation of the matrix. The cross sectional diameter of the treated graft remains less than the bone tunnel diameter (e.g., 8mm) and therefore able to slide freely into place where it will be fixed in place using interference screws, cross pins or other fixation means known to the art.

- [128] Figure 14 shows a variation of the previous embodiment where the chamber **140** is provided with a series of passageway holes **141** thereby allowing the graft to be placed and fixated dry, and to have activating solution applied to the exterior of the prepared graft *in situ*.
- [129] Figure 15a shows an example of a class of embodiments where a chamber containing a compressed matrix is fitted around the graft extracorporeally and filled with flowable biologically active agent *in situ*. A pleated chamber **150** with a fill-tube **151** is slid in place over the graft. Figure 15b shows a section of the embodiment at plane **152**, showing a series of pleated folds **154** around its circumference surrounding graft mid-section **123** and space filled with compressed matrix.
- [130] Figure 16 shows this same embodiment as it would appear in situ (joint and fixation means not shown) during injection of BAA. The intra-articular portion **160** of the chamber **150** expands as flowable biologically active agent is injected via syringe **161**, thereby expanding the compressed matrix and creating a large mass of therapeutic composition to provide increased cell growth and strength to the graft. In another embodiment the chamber is fitted around the graft and installed in the joint empty, and a flowable therapeutic composition, activated extracorporeally, is injected into the chamber.
- [131] Figure 17a shows an example of a class of embodiments including a wrap-around matrix with a barrier coating. When closed around the graft, the barrier sheet forms a chamber containing a matrix. Figure 17a shows a graft partially wrapped in the wrap-around

collagen sheet with a barrier coating **170**. Figure 17b is a detail view of Figure 17a showing individual collagen strips **171** held together by a barrier coating on the outside **172** of the sheet. The sheet is tied around the graft with sutures or other fasteners and the matrix is activated in any of the previously disclosed means (not shown). The activated wrap-around chamber can be used extracorporeally prior to graft implantation, or placed intracorporeally provided it is of sufficient length to fit inside the articular space.

[132] Figure 18 shows a typical arrangement of a knee **181** for arthroscopic surgery. An arthroscope **182** enters the joint through an anteriolateral portal or incision. An anterior cruciate ligament (ACL) **183** to be treated with a therapeutic composition can be accessed through an anteriomedial portal **184**.

[133] Figure 19 shows an embodiment of the present invention **190** comprising a hollow shaft **191** and terminating in a proximal end **192** and a distal end **193**. Distal end **193** includes a containment chamber **194**. Proximal end **192** includes a connector means **195** in communication with the lumen of hollow shaft **191** for attachment to a therapeutic composition preparation and advancing means, not shown. In other embodiments the therapeutic composition preparation and advancing means is integral to the device. In some embodiments, proximal end **192** further includes a control button **196** connected by a linkage (**204** in Figure 20a) for articulation of the containment chamber **194**. In some embodiments proximal end **192** further includes a connector means **197** for connection to a gas supply (not shown). Gas supply connector **197** communicated directly with containment chamber **194** through a secondary passage (not shown) running through shaft **191**.

[134] Figure 20a shows an embodiment of a containment chamber **194** at the distal end of the device. In this embodiment the entire containment chamber is molded in a flexible elastomer such as silicone rubber. The containment chamber **194** includes a fixed portion **200**, and an articulating portion **201** separated by a gap **202**. A linkage **204** connects to a control button (**196** in Figure 19) at the proximal end of the device. When actuated, the control button moves linkage **204** distally to flex articulating portion **201** as shown in Figure 20b, where gap **202** has closed completely. In practice, when used to treat an ACL with a therapeutic composition, the distal end **193** of device **190** is inserted into anteriomedial portal **184** of knee **181**. Containment chamber **194** is positioned with ACL **183** (not shown in fig 20a) in gap **202**. Control button **196** is actuated to close articulating portion **201** around ACL **183**. Top and bottom aligned openings **205** fit snugly around the ACL **183** leaving toroidal region **206** isolated from the surrounding environment of the knee joint which is filled with circulating saline fluid. At this point, therapeutic composition preparation and advancing means (not shown) can advance malleable composition through hollow shaft lumen **207** and into the toroidal region **206** surrounding the ACL, displacing any fluid that may be trapped in the toroidal region **206**. Alternatively, a gas such as air or carbon dioxide may be introduced into the toroidal region **206** to displace fluid prior to introduction of the therapeutic composition. Formulations of therapeutic composition that transition from a non-cohesive state to a cohesive state, where the cohesive state is impervious to saline, but the non-cohesive state is not, will require the chamber to remain closed around the ACL until the transition is complete, at which time the control button is again activated to open the articulating

portion **201**, releasing the ACL and leaving a cohesive mass of therapeutic composition encircling the full diameter of the ACL.

- [135] Figure 21a shows another embodiment of the present invention that has particular utility for the treatment of grafts used to reconstruct a torn ACL in the knee. The ACL reconstruction procedure involves drilling bone tunnels through the tibia and femur, passing a graft (allograft, autograft, or xenograft) through the tunnels, and fixing the tibial and femoral ends in place. In this embodiment the graft is passed through aligned openings **211** and **212** in containment chamber **210** prior to fixation of one or both ends. In practice, containment chamber **210**, being made of an elastomeric material like silicone, is collapsed and housed inside hollow shaft **191**, allowing it to be inserted into the joint through an anteriomedial portal. Once inside the joint the containment chamber **210** is ejected from the distal end of the hollow shaft **191** where it expands to its unconstrained shape as shown. To facilitate ejection and expansion, some embodiments include a network of spring wires **213**. The containment chamber **210** is next advanced into the intracondylar notch of the femur where openings **211** and **212** are aligned with previously drilled femoral and tibial bone tunnels respectively. The graft is passed through the tunnels such that the proximal end of the graft resides in the femoral tunnel and the distal end of the graft resides in the tibial tunnel, and the mid-section of the graft passes through the containment chamber **210** in the condylar notch. The surgeon then fixes the proximal and distal ends of the graft to the femur and tibia respectively. Like the embodiment in figure 20, therapeutic composition is then advanced into the containment chamber directly, displacing ambient fluid as it fills the structure, or in other embodiments, gas is introduced to displace fluid prior to advancing composition. Once

therapeutic composition has fully enveloped the mid section of the graft, and has transitioned from a non-cohesive state to a cohesive state, the containment structure may be removed. In an embodiment a seam **214** on the distal aspect of the containment chamber extending from opening **211** to opening **212** is held closed by a temporary closure, in this embodiment, a sewing stitch **215** that releases when one end of the thread is pulled. Other embodiments use other temporary closure means such as zippers, molded-in wires that tear the wall when pulled, thin wall sections or weak glue seams that fail under a pre determined load, or any of many other release mechanisms known to the art. Figure 21b shows the temporary closure released and seam **214** open, allowing the containment chamber to be pulled off the mass of cohesive therapeutic composition enveloping the graft. The containment structure **210** is then pulled back into the hollow shaft **191** and the device is removed from the joint. The therapeutic composition remains to treat the graft.

[136] Figure 22 shows an embodiment of the present invention **220**, comprising a hollow shaft chamber **221**, a handle **222**, a reservoir **223**, and a trigger lever **224**. The device has a proximal **225** and a distal **226** end. Although the distal end **226** is shown as being cylindrical, in the alternative, the distal end **226** may include a modified tip that would allow the composition to be extruded as a ribbon, an oval, or other polygonal configuration in cross-section.

[137] Figure 23a and 23b show this same embodiment of the device with one half of the handle housing removed to reveal the operating mechanism. In Figure 23A the reservoir **223** having integral ratchet teeth **230** has been inserted into the proximal end **225** of the

device where it engages with a drive mechanism comprising a pivoting and translating advancement arm **231** and a pivoting advancement ratchet pawl **232**. The advancement arm **231** includes a hook **233** engaging the reservoir ratchet teeth **230** and is attached to trigger lever **224**. The advancement ratchet pawl **232** also has a hook **234** engaging the reservoir ratchet teeth **230** and is attached to the handle housing **235** at a pivot **236**.

[138] Figure 23B shows the reservoir **223** advanced distally by means of squeezing the trigger lever **224**, causing the advancement arm **231** to translate in a distal direction, pulling the reservoir **223** with it. The pawl hook **234** clicks over the advancing reservoir ratchet teeth **230** until the trigger lever **224** reaches its maximum travel. The advancement pawl **232** then engages the reservoir ratchet teeth **230** preventing return motion in the proximal direction while the user relaxes her grip, allowing a return spring (not shown) to move the trigger lever **224** to its starting position, causing the advancement arm **231** to translate in the distal direction. At the end of its translation the advancement arm hook **233** re-engages the reservoir ratchet teeth **230** and the process is repeated. In this way, repeated squeezing of the trigger lever **224** causes the reservoir **223** to translate its full length in the distal direction.

[139] A cam **237** is provided such that when activated (turned 45° counter clockwise) it disengages the advancement arm **231** and the advancement ratchet pawl **232** and engages a retraction arm **238** and retraction pawl **239** that engage a set of retrograde ratchet teeth **240** on the reservoir **223**. In so doing, the mechanism is reversed and translation of the reservoir occurs proximally, allowing the device to draw fluids into the reservoir or release the reservoir from the device.

[140] Figure 24 shows a section view of the same embodiment of the device showing the internal components that affect the activation of the matrix to form a therapeutic composition and is ejection from the device. In this view we see a plunger **241** with a seal **242** attached to a hollow needle passageway **243**. The plunger, seal and needle passageway are attached to the handle housing **235** and do not translate. The reservoir **223** is shown in cross section revealing a fluid storage region **244**, filled with liquid biologically active agent, in communication with the inner lumen of the needle passageway **243**. As the reservoir is advanced in the distal direction by the advancement mechanism, fluid in the fluid storage region **244** is forced through the needle passageway. Also, as the reservoir **223** advances, it pushes against a pusher tube **245** that translates distally around the needle and through the shaft chamber **221**. The proximal portion of the pusher tube **245** has a slot that allows it to slide over a tang **246** that supports the needle and attaches the needle/plunger assembly to the handle housing **235**.

[141] Figure 25a, 25b and 25c show the distal portion of the same embodiment of the device shaft chamber **221** in cross section. Figure 25a shows the orientation of the device and the portion of the device (circled) detailed in Figures 25b and 25c.

[142] Figure 25b shows the hollow needle passageway **243** welded closed at its distal end **250** with a distributed series of transverse holes **251** near the distal end communicating with the inner lumen. Filling the space between the inner lumen of the shaft chamber **221** and the outer wall of the hollow needle passageway **243** are a series of tubular matrix segments **252**.

[143] Figure 25c shows the pusher tube **245** advancing distally, moving the tubular matrix segments **252** distally and eventually ejecting them from the distal end **16** of the device. Simultaneously to movement of the matrix segments, a biologically active agent is pumped from the reservoir, through the hollow needle passageway **243**, out the distributed series of transverse holes **251**, and into the pellets **252**, wetting them with a biologically active agent and thereby creating an activated therapeutic composition as it is being ejected from the device. The inside diameter of the reservoir **223** is designed such that 1 cm of translation of the reservoir inject the exact amount of a biologically active agent needed to activate 1 cm of matrix segment, thereby assuring the ideal desired ratio of matrix and a biologically active agent.

[144] Those skilled in the art will recognize that many other embodiments can be conceived that will achieve the same end function. Other embodiments substitute the ratcheting drive mechanism with a screw mechanism, hydraulic or pneumatic actuator, direct acting syringe-type plunger, motor drive, peristaltic pump, or any of the variety of means known for initiating movement of fluids and solids. Still other embodiments achieve ideal ratio of therapeutic composition components through the use of other than 1:1 drive means and instead use a plurality of drive means with different proportional rates of advancement. Still other embodiments provide for other combinations of components with different consistencies such as pastes, gels, foams, dry powders, liquids, etc. in any combination and number of components.

- [145] In another special embodiment of the invention, where the biologically active agent component of the therapeutic composition is autologously derived PRP, the additional means of processing whole blood to extract PRP is included as part of the invention.
- [146] Figure 26a, 26b and 26c are a schematic representation of one embodiment of an integral PRP extraction system incorporated into the device. Figure 26a shows a cross section of a schematic representation of a filter-based PRP extraction system. In an embodiment, cylindrical reservoir **260** takes the place of reservoir **223** in Figure 1. In one embodiment reservoir **260** is fixed relative to the handle **222**, and a first plunger with a first filter membrane **261**, and a second plunger with a second filter membrane **262**, move independently, each being driven by a separate trigger lever and reversing ratchet and pawl system (not shown, but like that comprised of items **224**, **231**, **232**, **237**, **238** and **239** shown previously), acting on first and second plunger/filter shafts **269** and **270**. A first passageway **263** communicate with the space between first plunger **261** and second plunger **262**. A second passageway **264** communicates with the space between the second plunger **262** and the right side wall of the reservoir **260**. The left side of the reservoir is filled with whole blood **265**.
- [147] Figure 26b shows first plunger with a filter membrane **261** moved to the left. The first filter membrane has a pore size sufficiently large to permit passage of platelets through the membrane but small enough to inhibit the passage of most red and white blood cells. The result of this filtering step is a region of concentrated red and white cells **266** and a region of plasma and platelets with 1x the concentration of platelets in whole blood **267**.

- [148] Figure 26c shows the second plunger with a second filter membrane **262** moved to the left. The second filter membrane has a pore size sufficient to prevent the passage of platelets while still allowing the passage of plasma. The result is a region with a volume of platelet rich plasma (PRP) **268** which may be extracted through first passageway **263** for use as the biologically active component of a therapeutic composition. Other embodiments eliminate the second plunger and second filter membrane **262** and use 1x PRP as the biologically active component of a therapeutic composition. The means of driving the plungers and extracting the PRP may be any of the mechanism means described above. In alternative embodiments, saline or other biologically neutral or inactive components may be used instead of or in addition to PRP.
- [149] Figure 27a shows an embodiment of a therapeutic compound dispensing element **271** of the present invention. The element **271** comprises a handle **272**, a trigger **273**, a syringe-like dispensing chamber **274**, and a delivery channel **275**.
- [150] Figure 27b shows the interior parts of the same element **271**, including a ratcheting mechanism **277** for advancing a piston **276** inside the chamber, and a sponge-like matrix **278** equipped with a central opening **279**.
- [151] Figure 28a shows an embodiment of the assembled invention, comprising the dispensing means **271**, a vacuum supply **280**, a valve manifold **281**, a switching valve **282** with a handle/direction indicator **284**, and a connector **283** for connecting to a reservoir of a liquid biologically active agent (not shown).

[152] Figure 28b shows interior components of the same invention, including passageway **285** passing through delivery channel **275** of dispensing component **271**, and into the central opening **279** of sponge-like matrix **278**. The portion of passageway **285** residing in central opening **279** is equipped with distributed radial holes **286** to uniformly distribute a liquid biologically active agent over the length of the sponge-like matrix. A leak-tight seal **287** engages the exterior of the delivery channel and the valve manifold to create an enclosed system. As shown in Figure 29, vacuum supply **280** communicates with switching valve **282** by means of a conduit **288**. The interior lumen of hollow tube passageway **285** communicates with switching valve **282** by means a conduit **289**. A reservoir of a liquid biologically active agent (not shown) connects to connector fitting **283** and communicates with switching valve **282** by means of a conduit **290**.

[153] In operation, an operator, usually the operating room scrub nurse, will open a sterile package containing the invention as shown in Figure 28a. The operator will connect a reservoir of, for example, liquid biologically active agent, or a syringe of autologous platelet rich plasma, or other biologically active or biologically neutral agents, to connector fitting **283**. The operator will then turn the handle/indicator **284** of switching valve **282** from its right-pointing “3-o’clock” storage position (shown in Figure 30a) counter clockwise to the “12-o’clock” position “1” (shown in Figure 30b), and in so doing connect vacuum supply **280** to chamber **274** containing sponge-like matrix **278** through conduits **288**, **289**, passageway tube **285**, and radial holes **286**. This will equalize the pressures of the vacuum supply and the sponge-like matrix **278**. The operator then turns the valve handle/indicator CCW to the “9-o’clock” position “2” (shown in Figure 30c). This action will first re-close conduit **288** to the vacuum supply, and then open

communication between the reservoir of liquid, biologically active agent connected to connector fitting **283** to the sponge-like matrix **278** by means of passageways **290**, **2894** passageway tube **285** and radial holes **286**. In doing so, the sponge-like matrix will become fully saturated in the absence of air. Piston **276** is advanced until pressure in chamber **274** is equalized with surrounding ambient pressure, compacting and concentrating the now activated therapeutic composition. The user then grasps the dispensing component **271**, pulling the delivery channel **275** out of the seal **287** into the valve manifold **281** and hands the dispensing component containing the activated therapeutic composition to the surgeon who delivers the composition to the patient's body.

[154] In an embodiment (shown) the vacuum supply **280** is an enclosed flask evacuated during manufacture of the device. In other embodiments the vacuum source may be a vacuum pump (manual or motorized), hospital wall suction, or simply a manually back-drawn syringe, or any other negative pressure sources known to the art. In an embodiment (shown) the switching valve **282** may be a cross-drilled stopcock. In other embodiments any of the multitude of multi-way valve types known to the art may be employed. In still other embodiments multiple single-way valves may be used to achieve the same effect. Still other embodiments employ different styles of dispensing means, tubes, advancing mechanisms, etc. all known to the art but achieving the same end result. Figure 31 shows another embodiment of the invention **331** including a chamber **312**, a proximal end cap **313** and a distal end cap **314** at the end of a delivery channel **315**.

[155] In section view Figure 32, we see the chamber **312** contains a matrix **321**. In an embodiment, matrix **321** consists of a dry porous sponge of matrix material. In an embodiment, the matrix material is substantially collagen, such as soluble Type I collagen. The chamber is sealed at the proximal end by an elastomeric septum/piston **322** and at the distal end by distal end cap **314** and the chamber containing the matrix is evacuated of all air during manufacture.

[156] Figure 33 shows activation of the matrix with a biologically active agent to form a therapeutic composition. In an embodiment a syringe containing a liquid biologically active agent **331** fitted with a needle **332** is inserted into elastomeric septum/piston **322**, thereby creating a passageway in communication with the chamber containing a matrix. A biologically active agent is either injected or simply drawn into the matrix by the vacuum within the chamber. The biologically active agent disperses into the matrix and activating the therapeutic composition.

[157] Figure 34a shows syringe **331** and needle **332** removed and the passageway created through elastomeric septum/piston **322** re-closed, leaving the chamber containing an activated therapeutic composition **346** and empty pores under vacuum. Elastomeric septum/piston **322** is held in position near the proximal end of the device by a latching mechanism **341** with a finger **342** engaging a notch **343** in the wall of chamber **312**.

[158] Figure 34b shows proximal end cap **313** removed. The cap includes a protuberance **344** that holds fingers **342** in notch **343** when attached to the chamber. With the cap unscrewed and removed from the chamber, a hinge **345** allows fingers **342** to swing

inward, disengaging notches **343** and allowing translational movement of the elastomeric septum/piston **322**. The activated therapeutic composition **346** within the chamber is porous, compressible and under vacuum. The free sliding septum/piston **322** responds to the pressure differential between the vacuum inside the chamber and atmospheric pressure outside by sliding into the therapeutic composition, collapsing the empty pores and compressing the composition until the pressure inside the chamber equalizes with atmospheric pressure outside. The final volume of the therapeutic composition equal to the solid volume of the matrix (less empty pore volume) plus the volume of biologically active agent added. The compressed volume contains virtually no air bubbles.

[159] Figure 35 shows another embodiment of the present invention comprising a body **351** with a screw thread connection element **352** for connecting the body **351** to device **311**. In the illustrated embodiment, a screw thread connection element **352**, a handle **353**, a ratcheted plunger **354**, and a trigger **355** act on the plunger **354**, such that squeezing the trigger **355** advances the plunger **354** distally (to the right) a small amount. A ratchet pawl and spring (not shown) prevent backward movement of the plunger **354** and return the trigger **355** so the process can be repeated over and over.

[160] Figure 36 shows the embodiment of the invention assembled and ready for use. Chamber **312** of device **311** screws onto component **351** with plunger **354** pushing against septum/piston **322** (not shown in this view). Distal end cap **314** is removed prior to use.

[161] Figure 37 shows the device in use. Delivery channel **315** is inserted into a body (not shown) with tissue to be treated. Trigger **355** is repeatedly squeezed and released, causing

plunger **354** to advance and push against septum/piston **322** (not shown in this view) which in turn extrudes activated therapeutic composition through the delivery channel and into the body. The delivered therapeutic composition **356** is free of entrapped air and does not sputter when extruded, is incompressible and therefore resistant to backflow of pressurized irrigation fluid (e.g. saline in arthroscopy), and is neutrally buoyant and does not float to the top of the fluid in the body.



## CLAIMS

What is claimed is:

1. A therapeutic capsule having an outer element defining an interior chamber and including a matrix disposed therein.
2. A therapeutic capsule according to claim 1, wherein the interior chamber is elongated along a chamber axis.
3. A therapeutic capsule according to claim 2, wherein the matrix includes a cylindrical central void region having a diameter D and extending from at least a first end thereof and along the chamber axis.
4. A therapeutic kit comprising,
  - A. a therapeutic capsule according to claim 3, and
  - B. an introducing device adapted to introduce a fluid biologically active agent to the matrix.
5. A therapeutic kit according to claim 4, wherein the introducing device includes a cylindrical elongated delivery element disposed about a central void region extending along a delivery axis from a proximal end to a distal end thereof, and having a cylindrical outer surface extending from the distal end along the delivery axis, and having a diameter less than or equal to D,

wherein the central void region is adapted at the proximal end to receive the fluid biologically active agent, and

wherein the delivery element includes one or more radially extending holes near the distal end and extending between the outer surface and the central void region.

6. A therapeutic kit according to claim 5,

wherein the introducing device is a syringe having an elongated reservoir element disposed about a reservoir region and extending from a proximal end to a distal end along the delivery axis, and having a piston disposed in the reservoir element near the proximal end, and having a cap at the distal end thereof, wherein the reservoir region is disposed between the piston and the cap, and wherein the cylindrical elongated delivery element extends from the cap whereby the central void region is in fluid communication with the reservoir region.

7. A therapeutic capsule according to claim 2, wherein the outer element defines the chamber to be closed and fully enclosing the matrix.

8. A therapeutic capsule according to claim 2, wherein the outer element defines the chamber to be open-ended, having a first open end along the chamber axis at one end thereof, and a second open end along the chamber axis opposite thereto.

9. A therapeutic capsule according to claim 2, wherein the outer element includes a longitudinal slit therein, and wherein the matrix is longitudinally segmented, wherein each segment extends radially inward from the outer element and is tapered in a radial direction.

10. A therapeutic capsule according to claim 8, wherein the outer element includes one or more through holes extending radially therethrough.
11. A therapeutic capsule according to claim 4, wherein the outer element is longitudinally segmented into a plurality of segments extending in a direction substantially parallel to the chamber axis.
12. A therapeutic capsule according to claim 5, wherein the power element is longitudinally segmented into two segments, each of the segments having C-shaped cross-sections along the chamber axis.
13. A therapeutic capsule according to claim 1, wherein the outer element is bioabsorbable.
14. A therapeutic capsule according to claim 7, wherein the outer element is composed of one from the group consisting of gelatin, sugar, cellulose, and polymer.
15. A therapeutic capsule according to claim 1, wherein the outer element includes an elongated extension extending therefrom, wherein the elongated extension defines an interior region in fluid contact with the chamber.
16. A therapeutic capsule according to claim 8, wherein the elongated extension is flexible.

17. A therapeutic capsule according to claim 1, wherein the matrix is compressible and the outer element is flexible.
18. A therapeutic capsule according to claim 11, wherein the matrix is dry and porous.
19. A therapeutic capsule according to claim 12, wherein the dry porous matrix is a sponge.
20. A therapeutic kit comprising a therapeutic capsule according to claim 1, and an introducing device adapted to introduce a fluid biologically active agent to the matrix.
21. A therapeutic kit comprising a therapeutic capsule according to claim 14, wherein the introducing device is a syringe.
22. A therapeutic kit according to claim 14 wherein the biologically active agent comprises one from the group consisting of whole blood, platelet-rich plasma (PRP), and saline.
23. A therapeutic kit according to claim 22 wherein the matrix is responsive to introduction of the PRP to become amorphous.
24. An activation device for a therapeutic compound, comprising:  
an outer element defining an interior chamber and including a dry porous collagen matrix disposed therein,  
wherein the outer element defines the chamber to be closed and fully enclosing the matrix, and

wherein the chamber is characterized by a static pressure above or below ambient, and  
wherein the outer element is adapted to receive a delivery element for infusing said matrix with a biologically active agent.

25. A therapeutic kit for a therapeutic compound, comprising:

- A. an activation device according to claim 24, and
- B. an introducing device adapted to introduce a fluid biologically active agent through the outer element and into the matrix.

26. An activation device for a therapeutic compound comprising:

an outer element defining a cylindrical interior chamber extending along a central axis, the chamber having a piston disposed at one end thereof, and being sealed at the other end thereof, the chamber including a dry porous matrix disposed therein, further including a selectively operative latch assembly, operative in a first state to fixedly hold the piston in the chamber, and operable in a second state to release the plunger allowing motion of the plunger in the chamber along the central axis in response to a pressure differential across the plunger, and

wherein the chamber is characterized by a static pressure below ambient, and  
wherein the piston is adapted to receive a delivery element for infusing the chamber with a biologically active agent.

27. An introducer for allowing passage therethrough of a compressible cylindrical therapeutic capsule disposed on an axial extending suture, comprising:

a tube extending along an introducer axis from a proximal end to a distal end,  
wherein the tube is characterized by a monotonically increasing diameter from the proximal end to the distal end, and  
wherein the tube included a longitudinal slit extending from the proximal end to the distal end.

28. A delivery kit for delivering a therapeutic compound including a cylindrical, suture-bearing, dry porous matrix composed of a collagen matrix, comprising:

- A. an outer elongated element having a length  $L1$  and extending from a proximal end to a distal end along a delivery axis, and defining an inner cylindrical region,
- B. an inner elongated element having a length  $L2$ , where  $L2$  is greater than  $L1$ , and disposed slidably within the inner cylindrical region of the outer elongated element, and extending from a proximal end to a distal end along the delivery axis, and defining an inner cylindrical region having diameter  $D1$ ,
- C. a pusher assembly extending along a pusher axis from a matrix pusher element at a proximal end to a control pusher element at a distal end,

wherein at least the matrix pusher element at the distal end is adapted to be slidable within the inner cylindrical region of the inner elongated element with the pusher axis being substantially coaxial with the delivery axis, wherein the matrix pusher element extends transverse to the pusher axis and wherein the pusher element has a circumferential edge has a diameter slightly less than  $D1$  and includes a plurality of void regions extending radially inward from the circumferential edge, and  
wherein the control pusher element is rigidly coupled to the matrix pusher element by an intermediate element, and

- D. a plurality of elongated suture capture devices, each suture capture device extending along a suture device axis from a handle portion at a proximal end to a suture capture portion at a distal end, and having a length greater than L2.
29. A therapeutic composition containment device comprising:
- A. an elongated primary shaft extending from a proximal end to a distal end along a shaft axis, defining a primary interior region extending along said shaft axis from said proximal end to said distal end,
  - B. a containment structure extending from said distal end of said elongated shaft and having two states:
    - i. a first state wherein said containment structure is C-shaped and disposed about a central axis transverse to said shaft axis, and extends between opposite ends thereof and defining a gap between said opposite ends, and
    - ii. a second state wherein said containment structure is ring-shaped and disposed about said central axis, said ring-shaped containment structure having an innermost surface defining an open faced circular channel extending circumferentially about said central axis, said channel being in fluid communication with said interior region of said shaft.
30. A containment device according to claim 29, wherein said central axis intersects with and is perpendicular to said shaft axis.

31. A containment device according to claim 29, wherein said device includes a state control assembly selectively operable from said proximal end to control said containment structure to be in said first state with said gap being substantially closed and in said second state with said gap being opened and having a predetermined non-zero value.

32. A containment device according to claim 31, further comprising:  
an outer elongated shaft disposed along an outer axis and defining an interior region extending along said outer axis, said outer elongated shaft being adapted to overfit said primary elongated shaft with said outer axis substantially parallel with said shaft axis, whereby said primary elongated shaft slides within said outer elongated shaft, and  
wherein said containment structure is compressible to permit positioning within said interior region of said outer elongated shaft.

33. An apparatus for loading a therapeutic composition, said therapeutic composition including a matrix and a biologically active agent (BAA), comprising:

- A. a delivery device, defining an interior cylindrical mixing chamber extending along a central axis between a proximal end and a distal end, and including at said distal end, a delivery tube extending therefrom along said central axis from said distal end to a delivery tip, said delivery tube defining an interior region extending along said central axis and having length L and a minimum dimension D transverse to said central axis and being in fluid communication with said Interior mixing chamber,

- B. an activation assembly including a housing having a vacuum (VAC) port, a biologically active agent (BAA) port, and a loading port and a valve, wherein said VAC port, said BAA port and said loading port are coupled to said valve, wherein said valve is operative in a first state to couple said VAC port to said loading port, and in a second state, to couple said BAA port to said loading port, and
- C. an elongated mixing tube coupled to and extending from said loading port, said mixing tube defining an interior BAA flow region extending along a BAA loading axis between said loading port and a distal end of said mixing tube.
34. An apparatus according to claim 33, wherein the length of said BAA flow region is greater than L, and wherein said mixing tube includes a plurality of radially extending holes disposed near said distal end of said mixing tube, said holes coupling said BAA flow region to points outside said mixing tube, wherein the maximum diameter of said mixing tube is less than D.
35. An apparatus according to claim 33, further comprising a vacuum supply coupled to said VAC port.
36. An apparatus according to claim 33, further comprising a BAA reservoir coupled to said BAA port.
37. An apparatus according to claim 33, further comprising a piston disposed in said cylindrical mixing chamber and an associated driver, said piston being adapted for motion along said central axis in response to user-controlled action on said driver.

38. An apparatus according to claim 33, further comprising a seal at said loading port for receiving said delivery tip, whereby said interior region of said delivery tube is in fluid communication with said loading port, with said mixing tube disposed within said delivery tube with said central axis being substantially coaxial with said BAA loading axis.

39. An apparatus for loading a therapeutic composition, said therapeutic composition including a matrix and a biologically active agent (BAA), to a delivery device whereby said matrix and said BAA are intermixed.

40. An activation and dispensing kit for a therapeutic compound, comprising:

- A. a biologically active agent (BAA) container defining an interior BAA region extending from a closed proximal end to an elongated, cylindrical open distal end having a diameter R disposed about a BAA axis, and including a BAA coupler at the open distal end, and
- B. an activator/dispenser including:
  - a. a housing,
  - b. an elongated dispensing tube defining an elongated cylindrical dispensing region extending from the housing to an open distal end along a dispensing axis A,
  - c. an elongated hollow needle extending from the housing, and defining an interior needle region extending from a proximal end within the housing to a closed distal end within the dispensing tube, wherein the dispensing tube and the hollow needle are coaxial along axis A, and define an annular matrix reservoir region in the dispensing region between the dispensing

tube and the needle, and wherein the needle includes at or near its distal end, one or more holes coupling the interior needle region with the matrix reservoir region,

- d. an elongated matrix pusher having an annular proximal end having an outer diameter greater than R and an extended elongated distal end extending therefrom coaxial along axis A, wherein the distal end is disposed in the matrix reservoir region,
- e. a central bore disposed in the matrix reservoir region and extending from an annular proximal end having an outer diameter greater than R,
- f. a BAA coupling assembly affixed to the proximal end of the needle, including an annular resilient seal having diameter R and disposed about the proximal end the interior needle region, the BAA coupling assembly being adapted to receive the BAA container whereby the BAA axis is coaxial with the dispensing axis A and the interior BAA region is fluidly coupled to the interior needle region, and
- g. an actuator assembly including means for advancing a BAA container coupled to the BAA coupling assembly about the seal, whereby the open end of the BAA container is translated in the direction of the dispensing axis A.

40. A kit according to claim 39, wherein the advancing means of the actuator assembly is selectively operative in a first state to advance a BAA container toward the distal end of the

dispensing tube and in a second state to advance a BAA container away from the distal end of the dispensing tube.

41. A kit according to claim 40, wherein the advancing means is a selectively bidirectional ratcheting assembly.

42. A kit according to claim 39, wherein the one or more holes coupling the interior needle region with the matrix reservoir region, are a plurality of radially extending holes extending from points near the distal end.

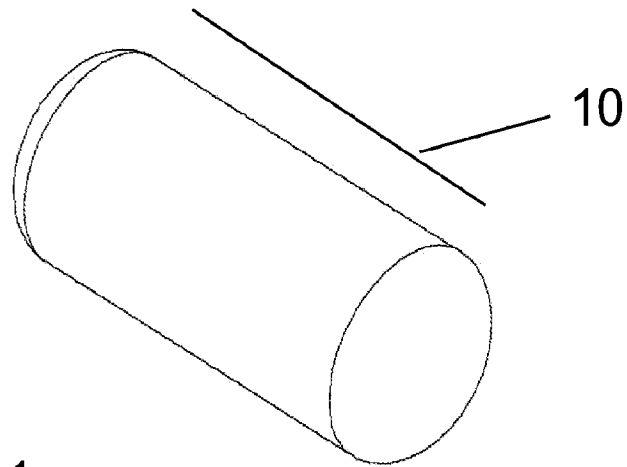


Figure 1a

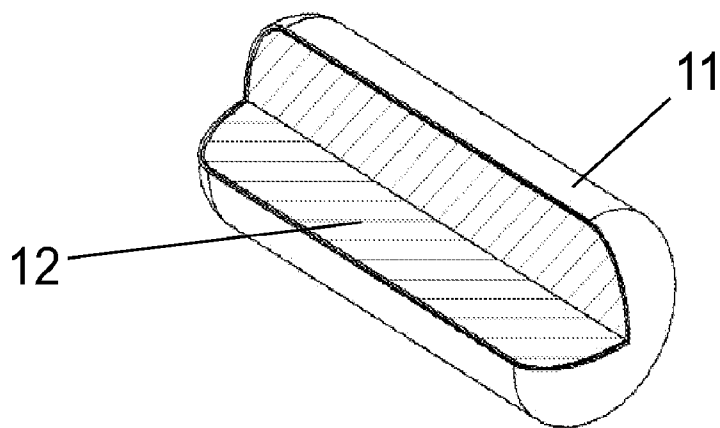


Figure 1b

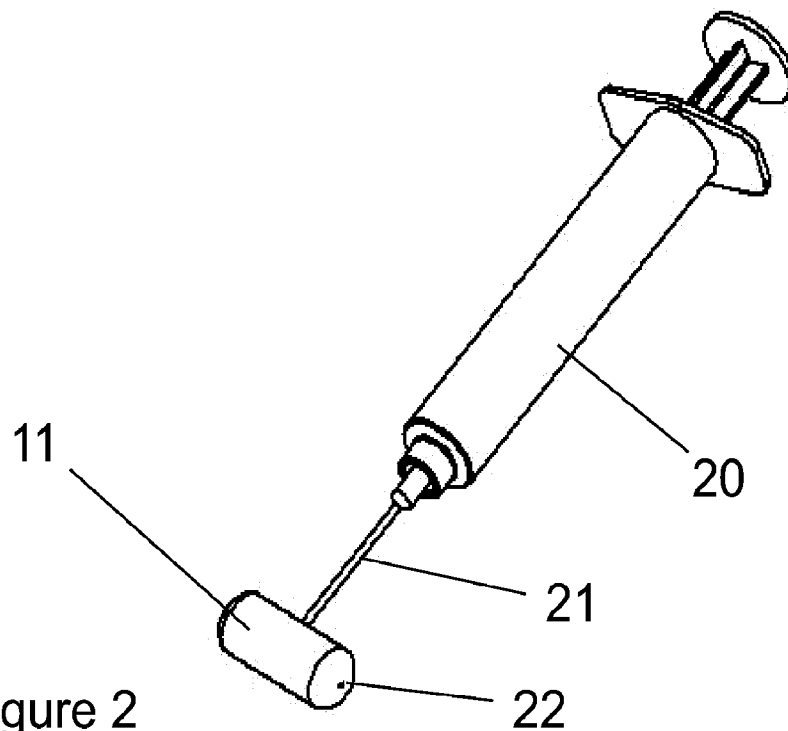


Figure 2

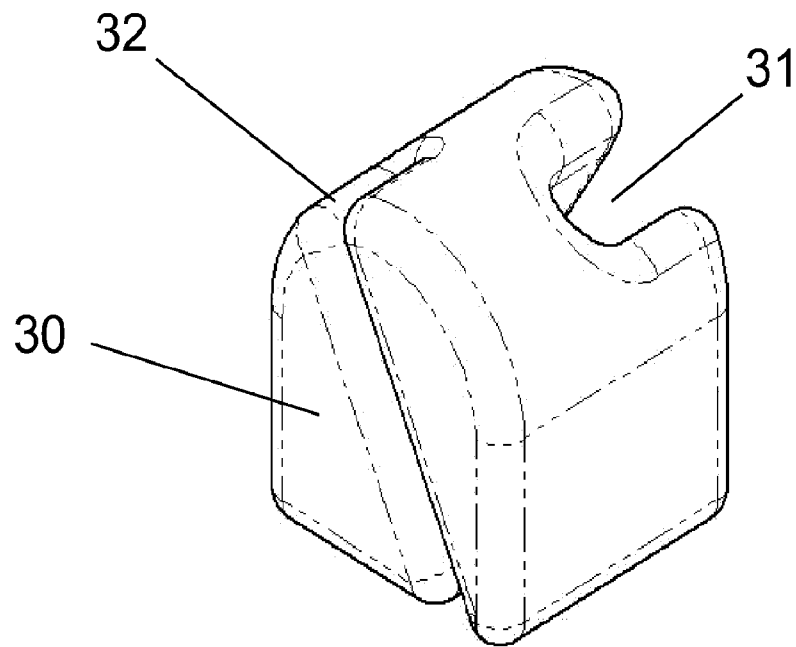


Figure 3

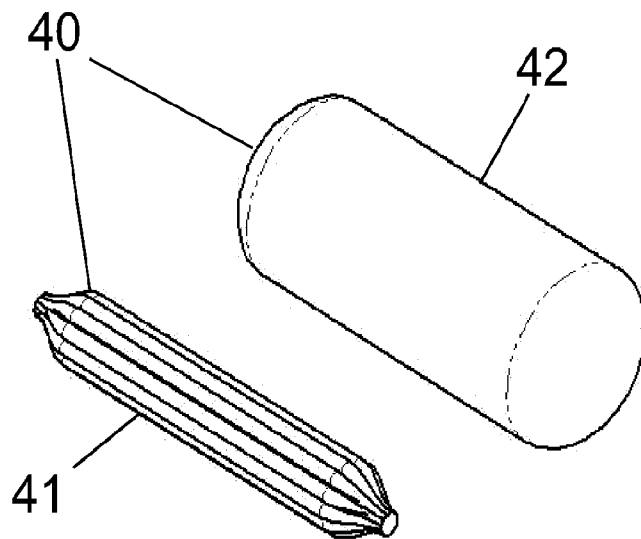


Figure 4A

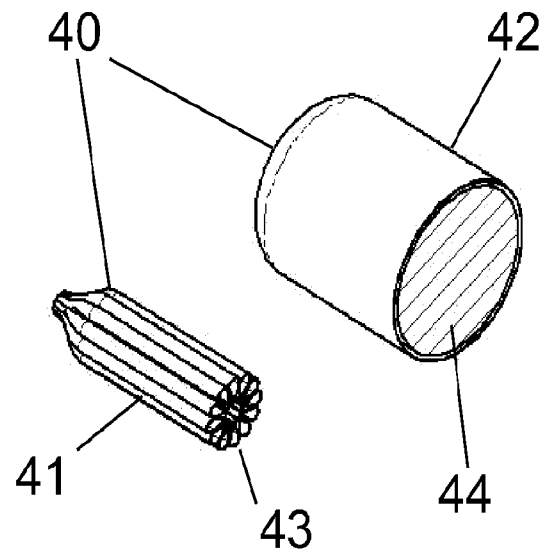


Figure 4B

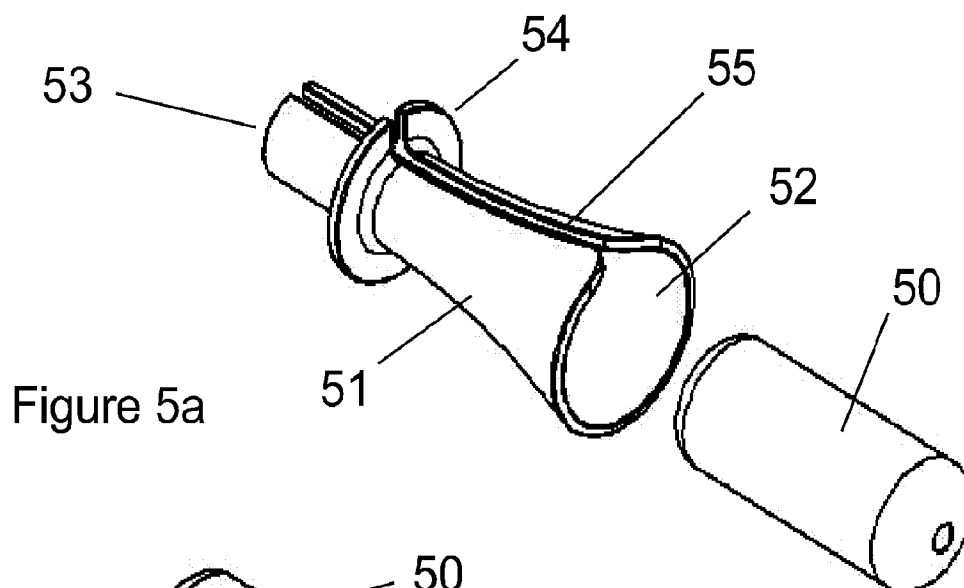


Figure 5a

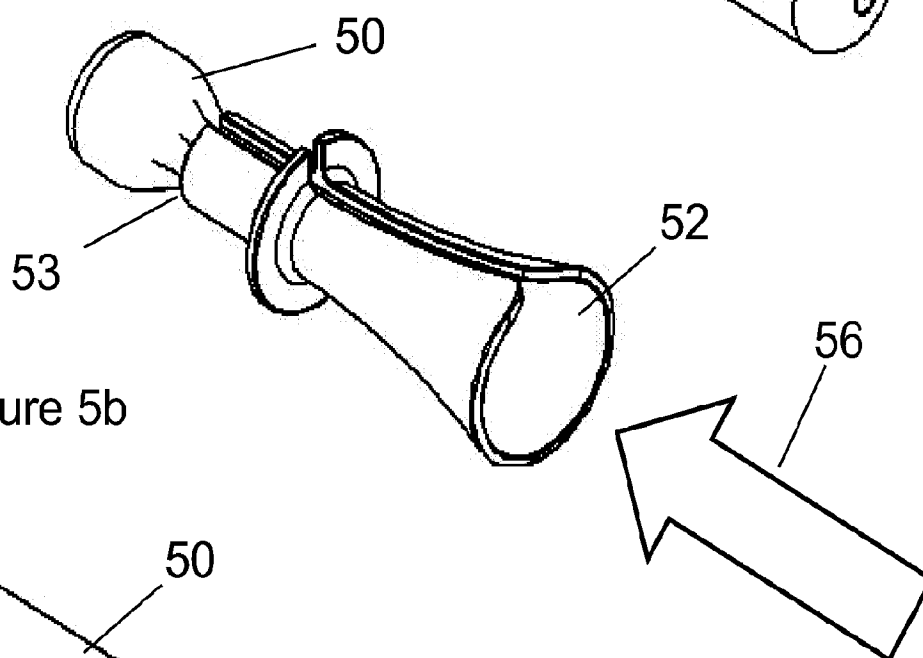


Figure 5b

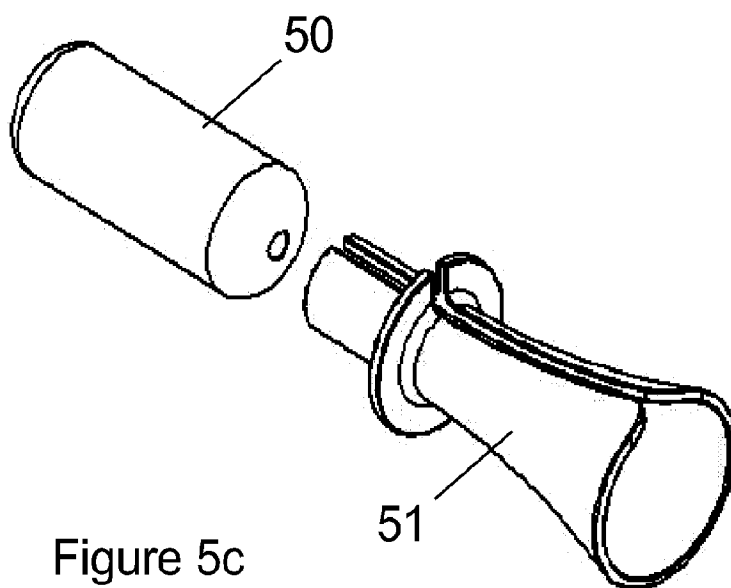
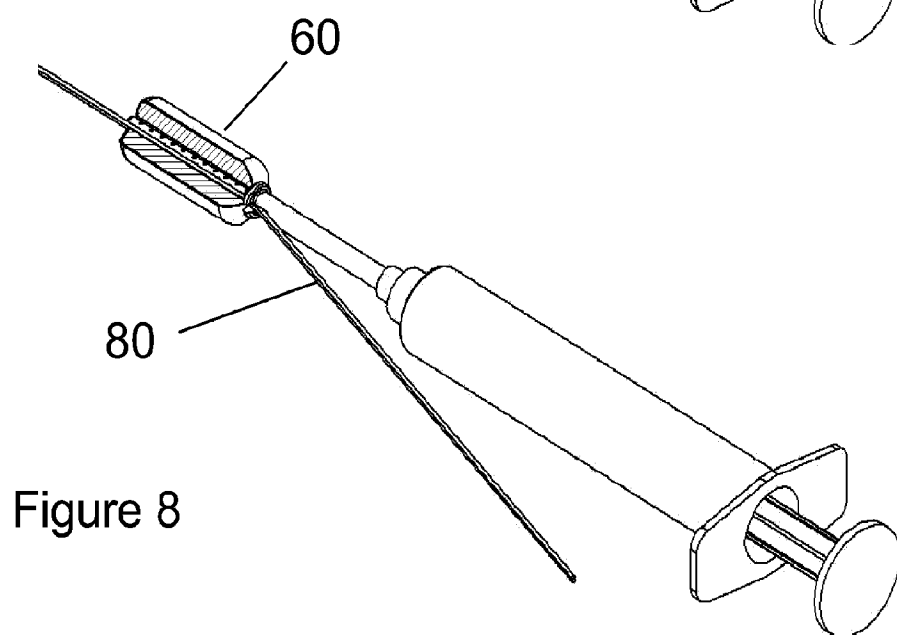
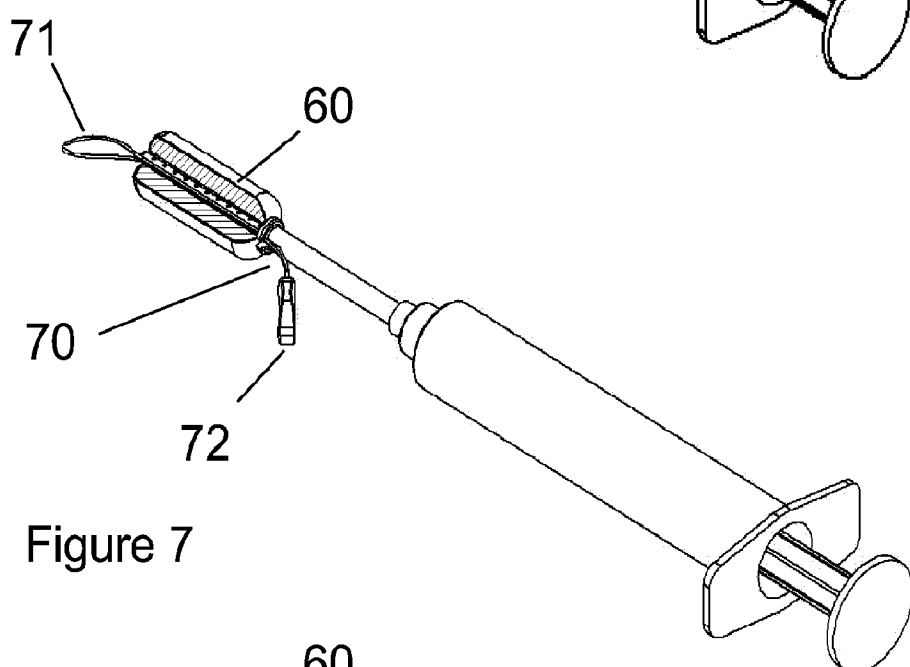
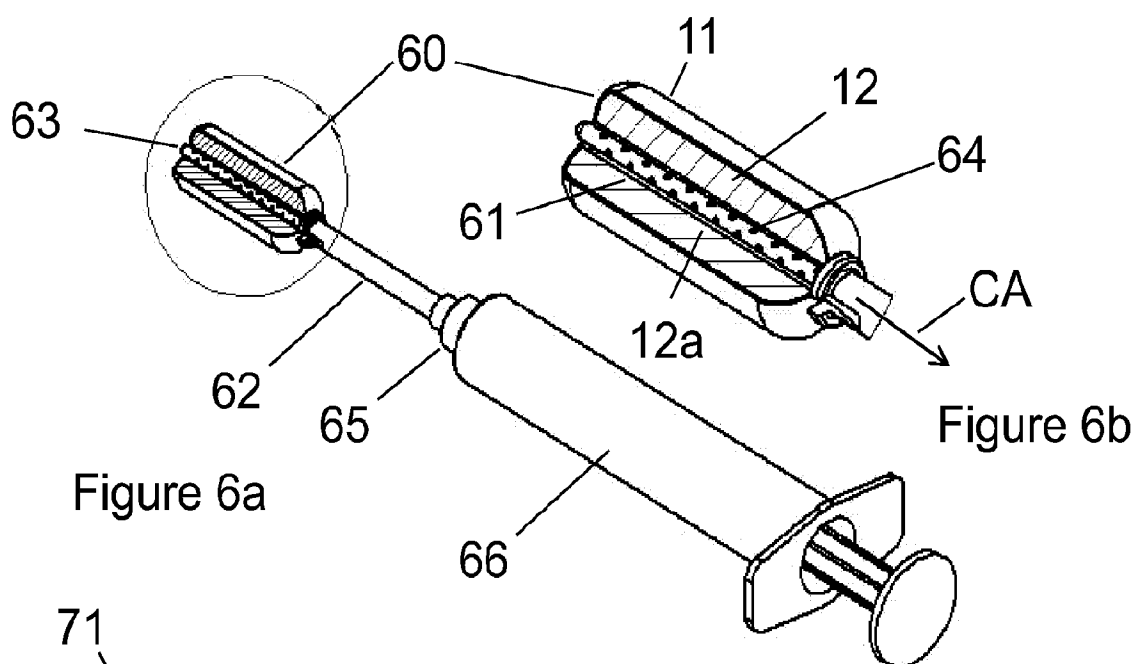


Figure 5c



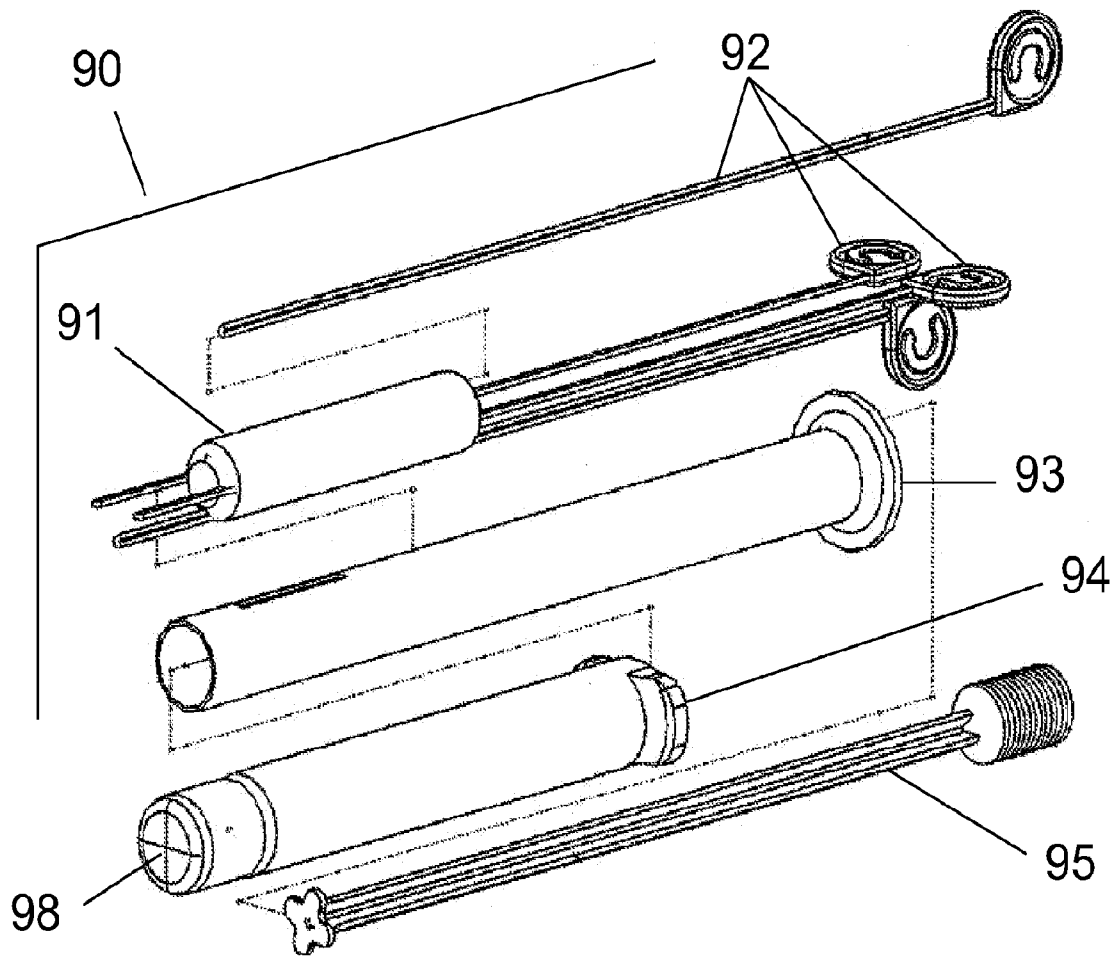


Figure 9a

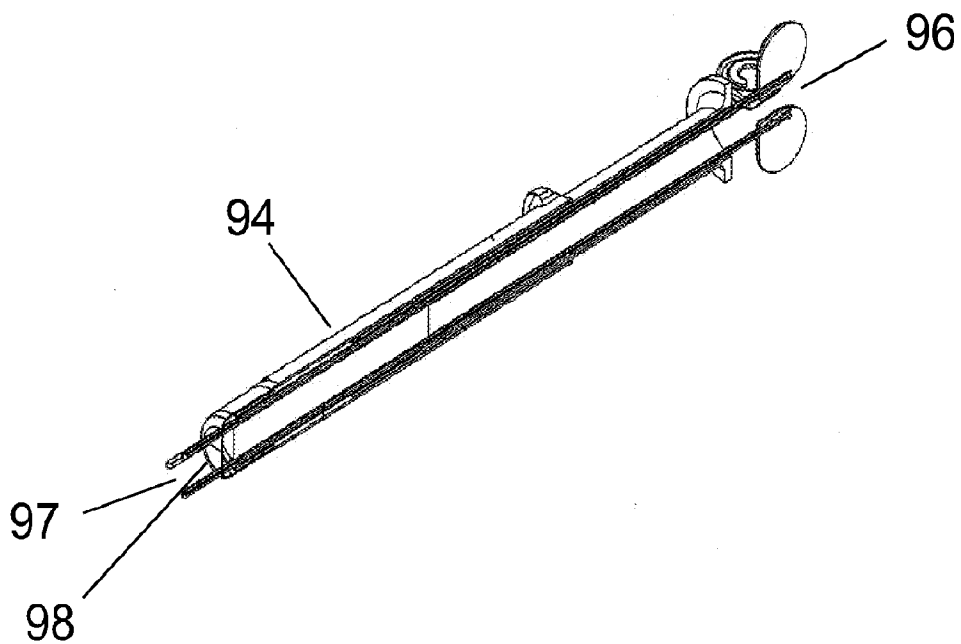


Figure 9b

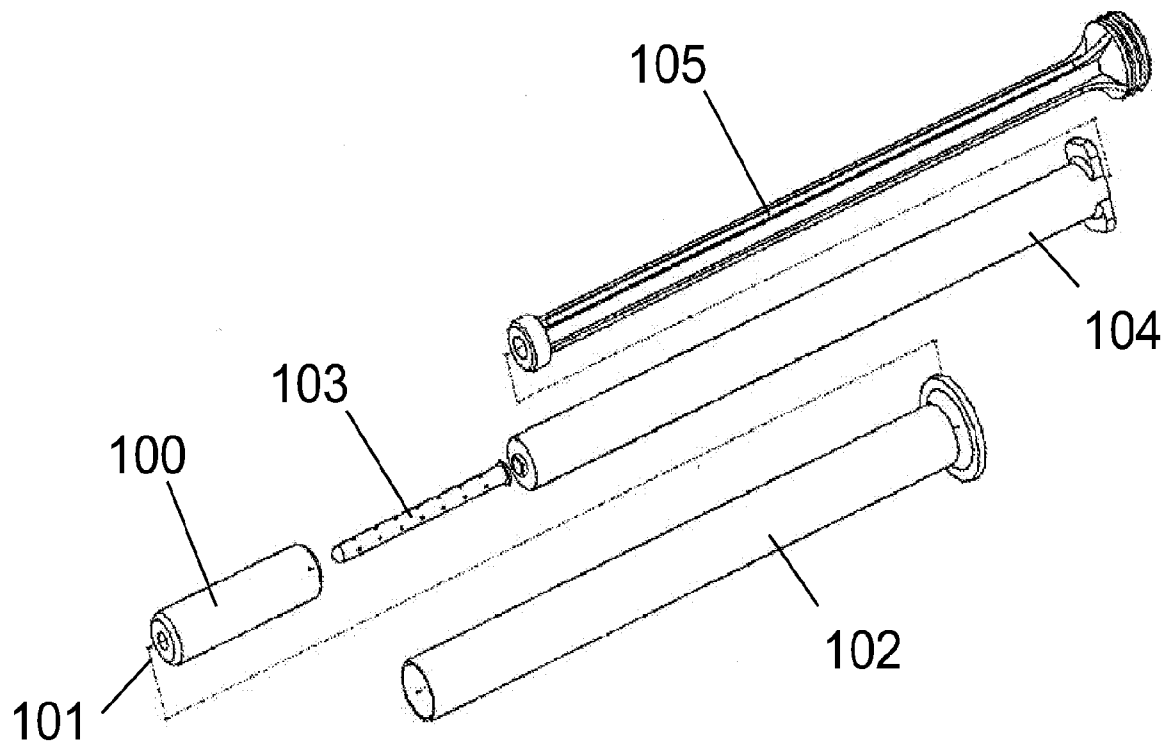


Figure 10a

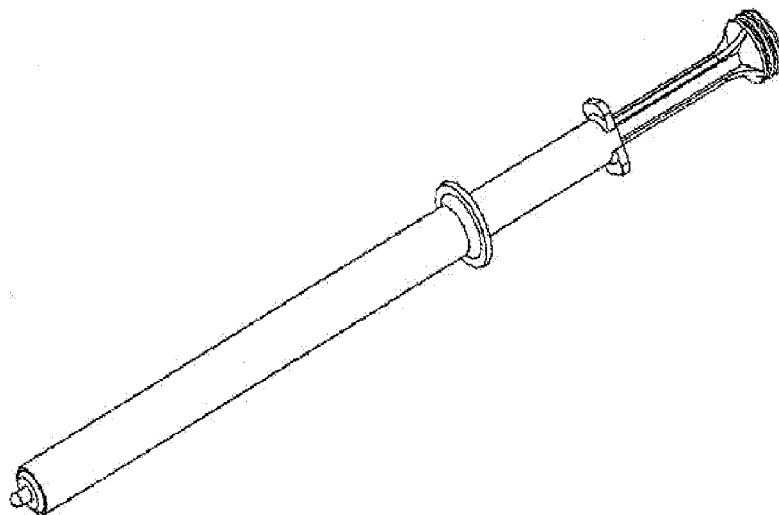


Figure 10b

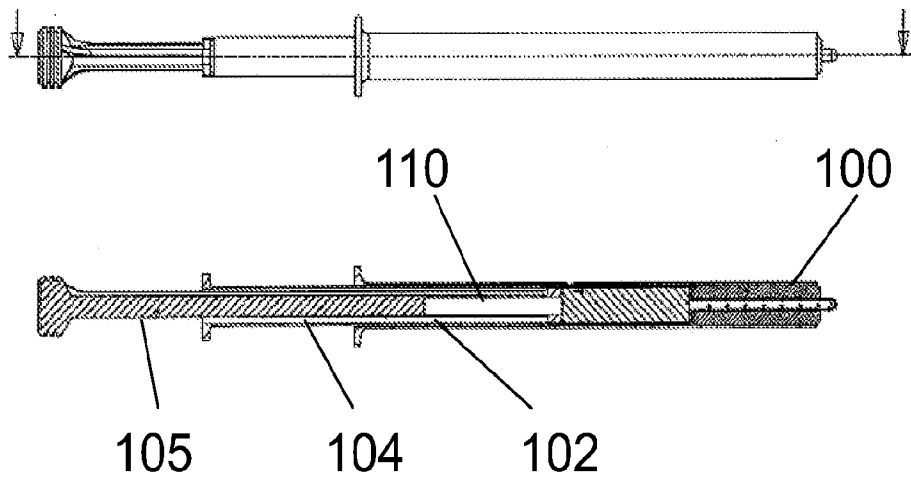


Figure 11a

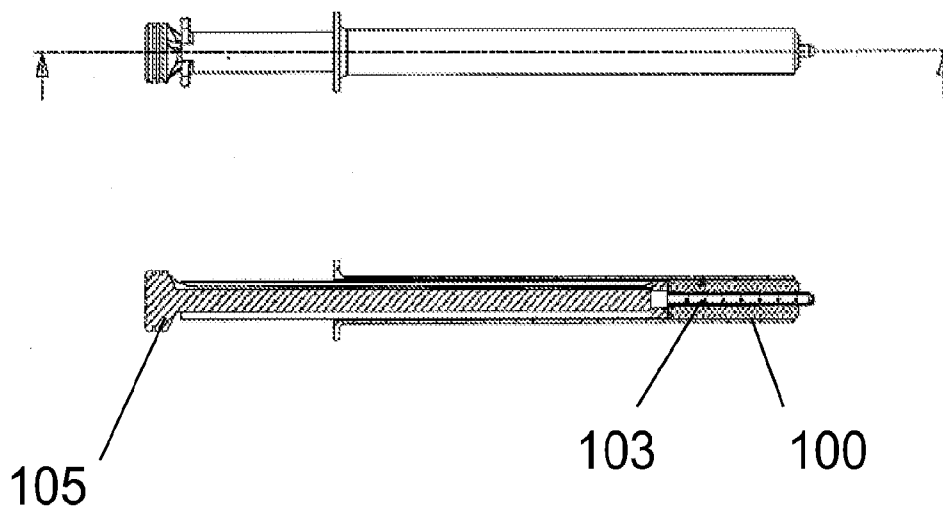


Figure 11b

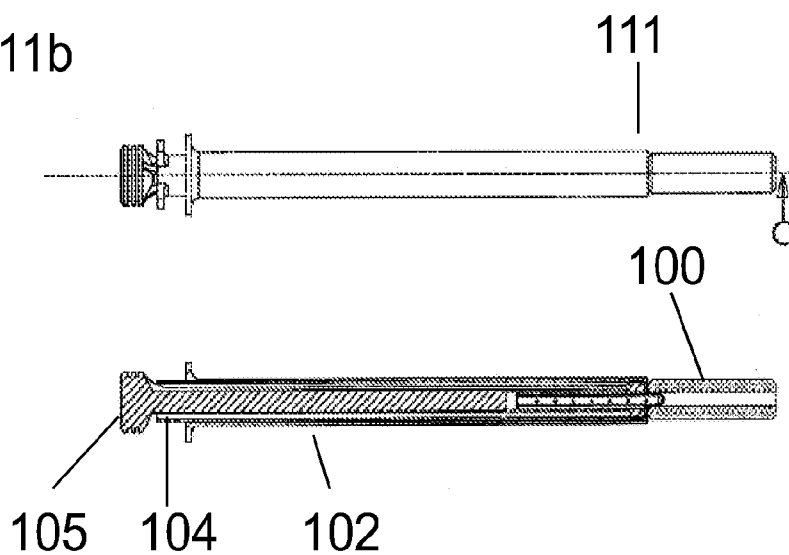
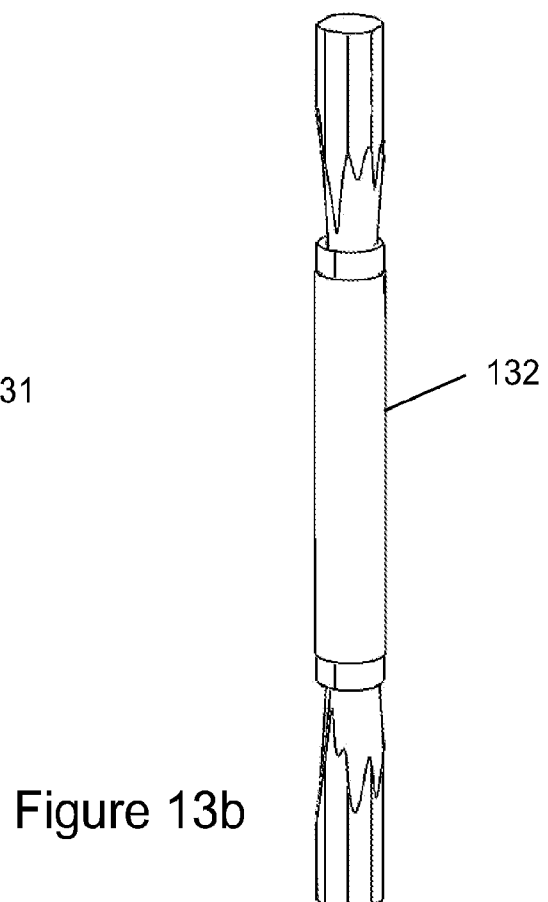
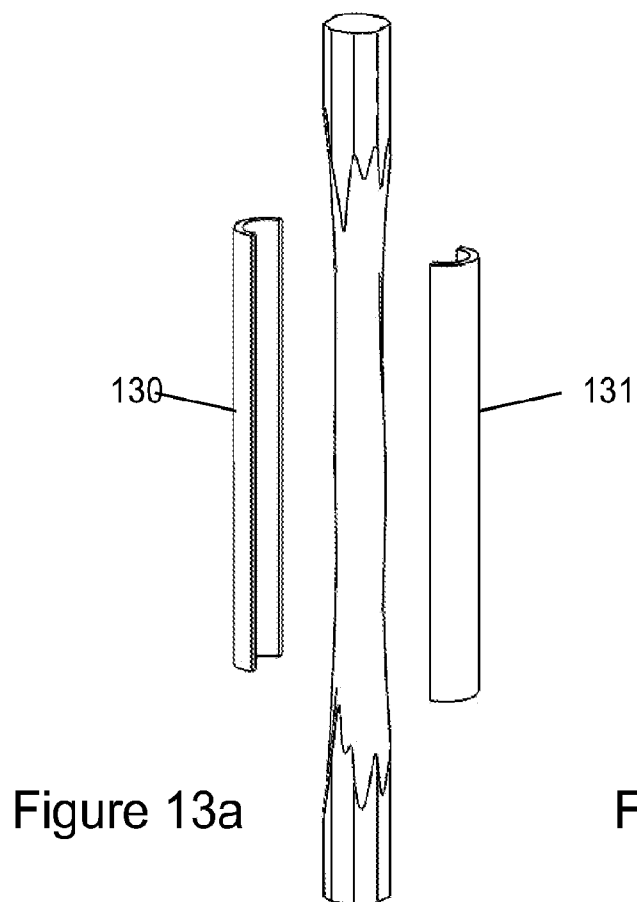
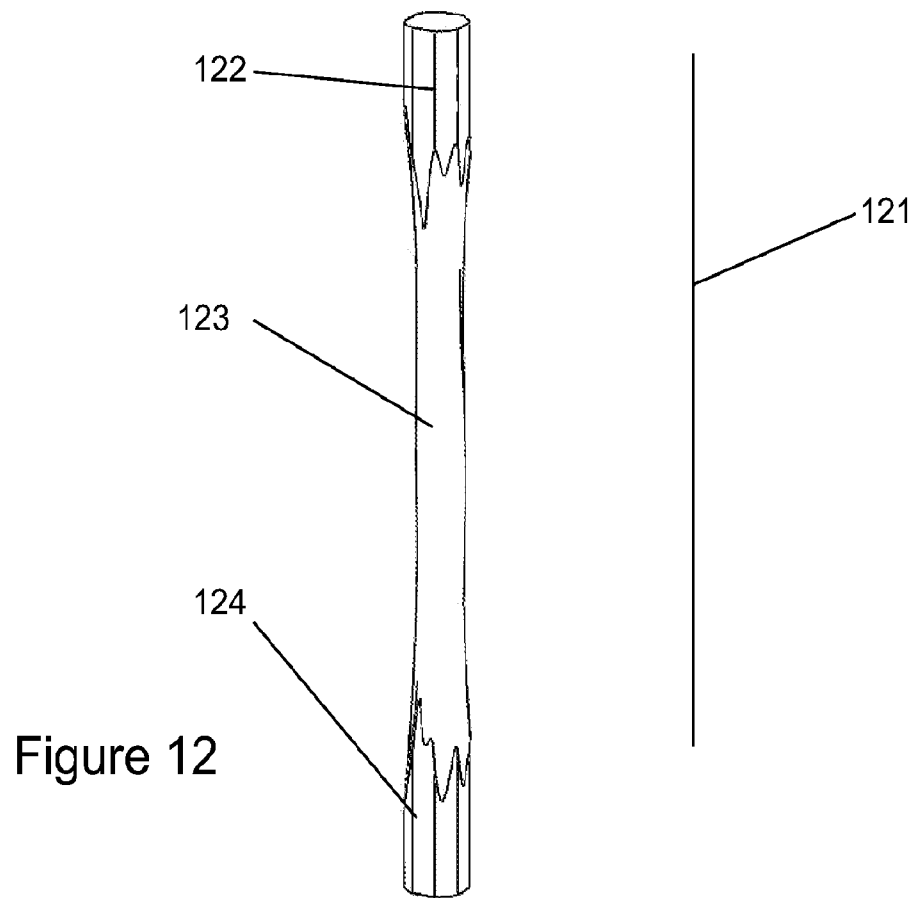


Figure 11c



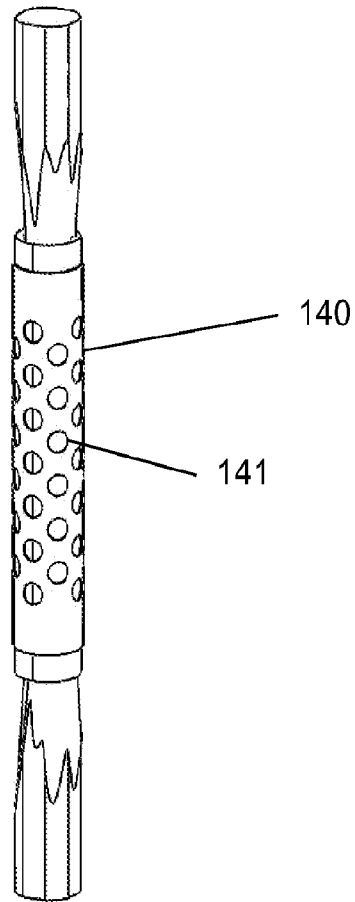


Figure 14

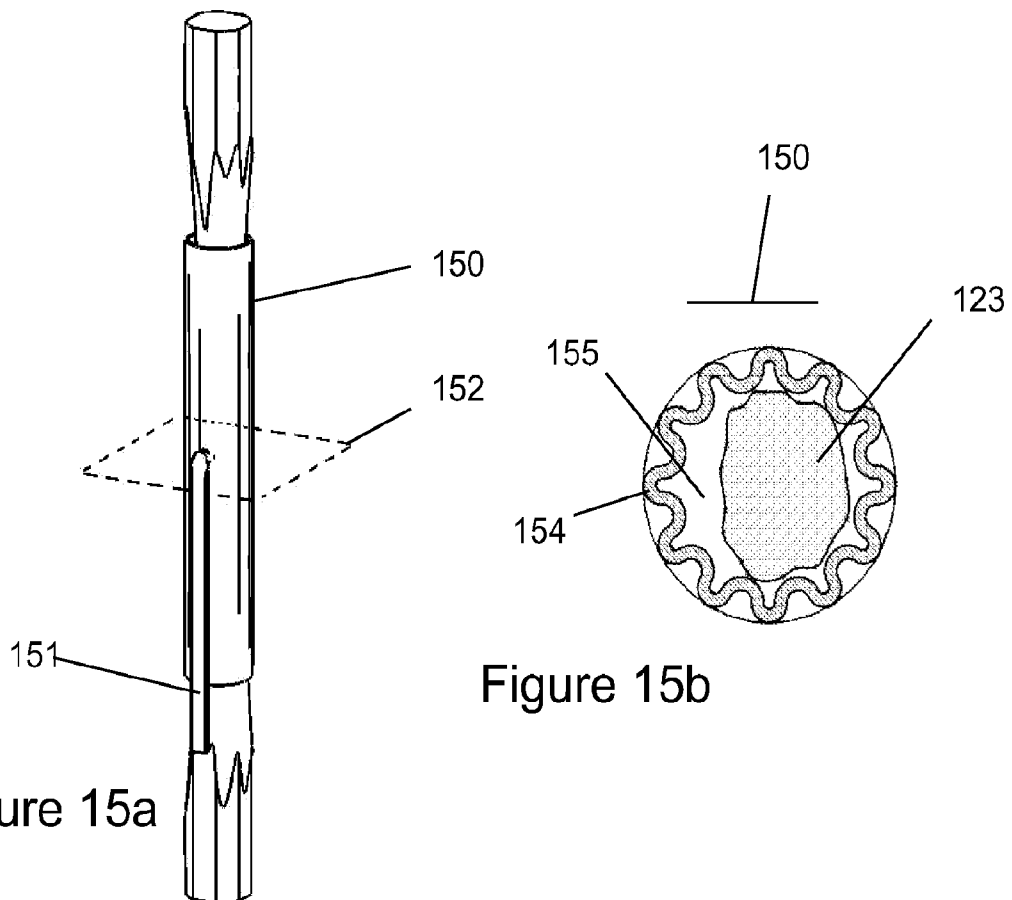


Figure 15b

Figure 15a

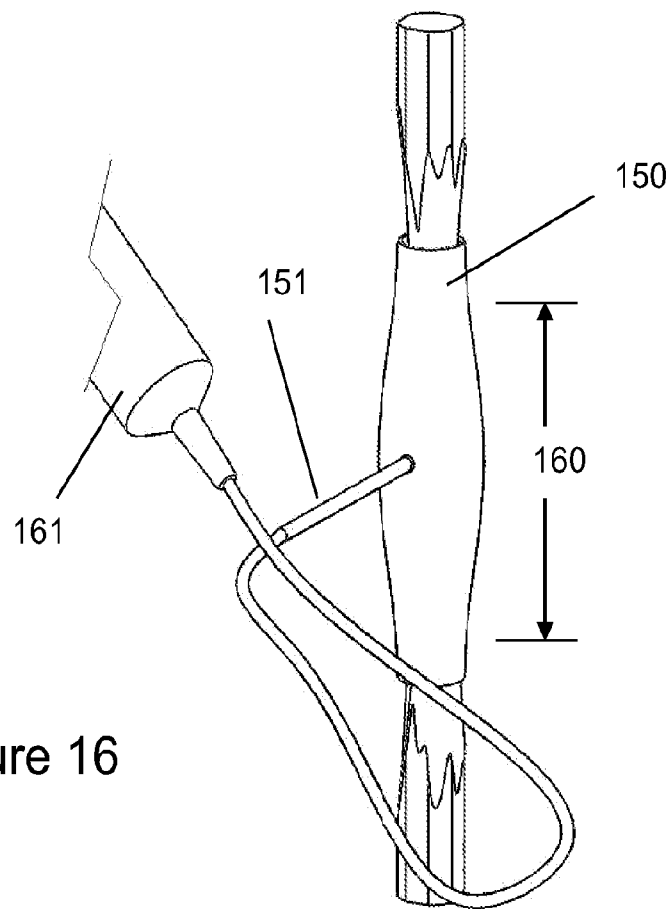


Figure 16

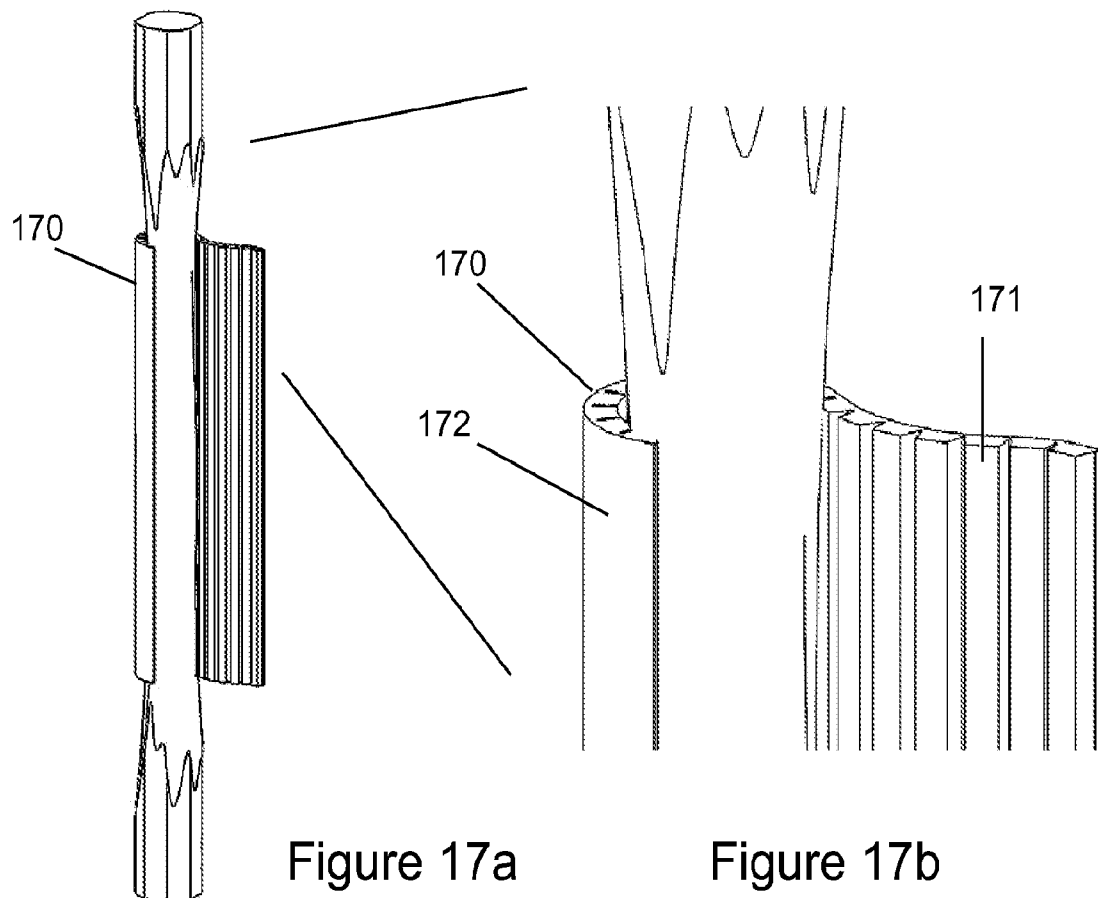


Figure 17a

Figure 17b

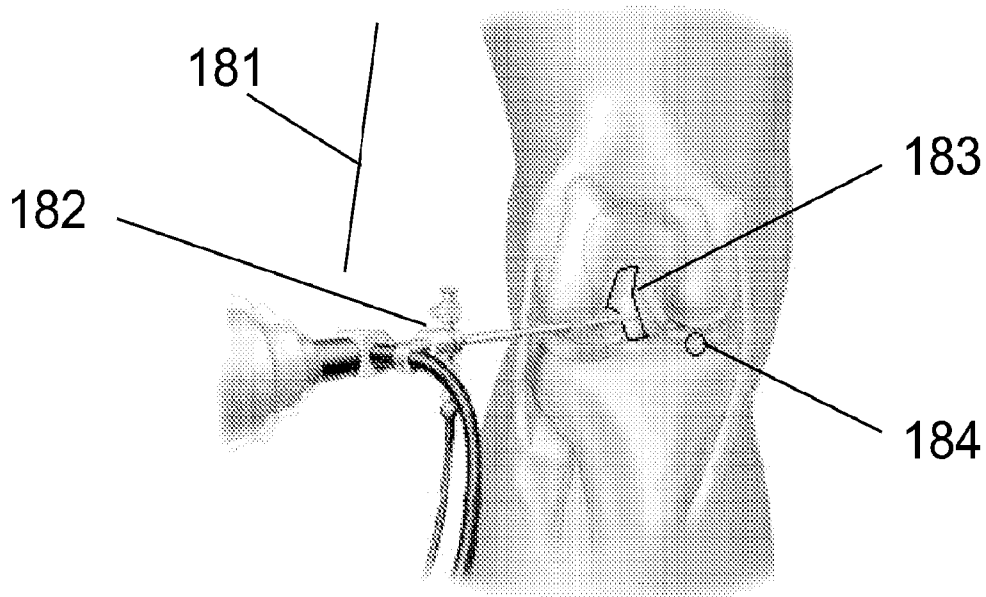


Figure 18

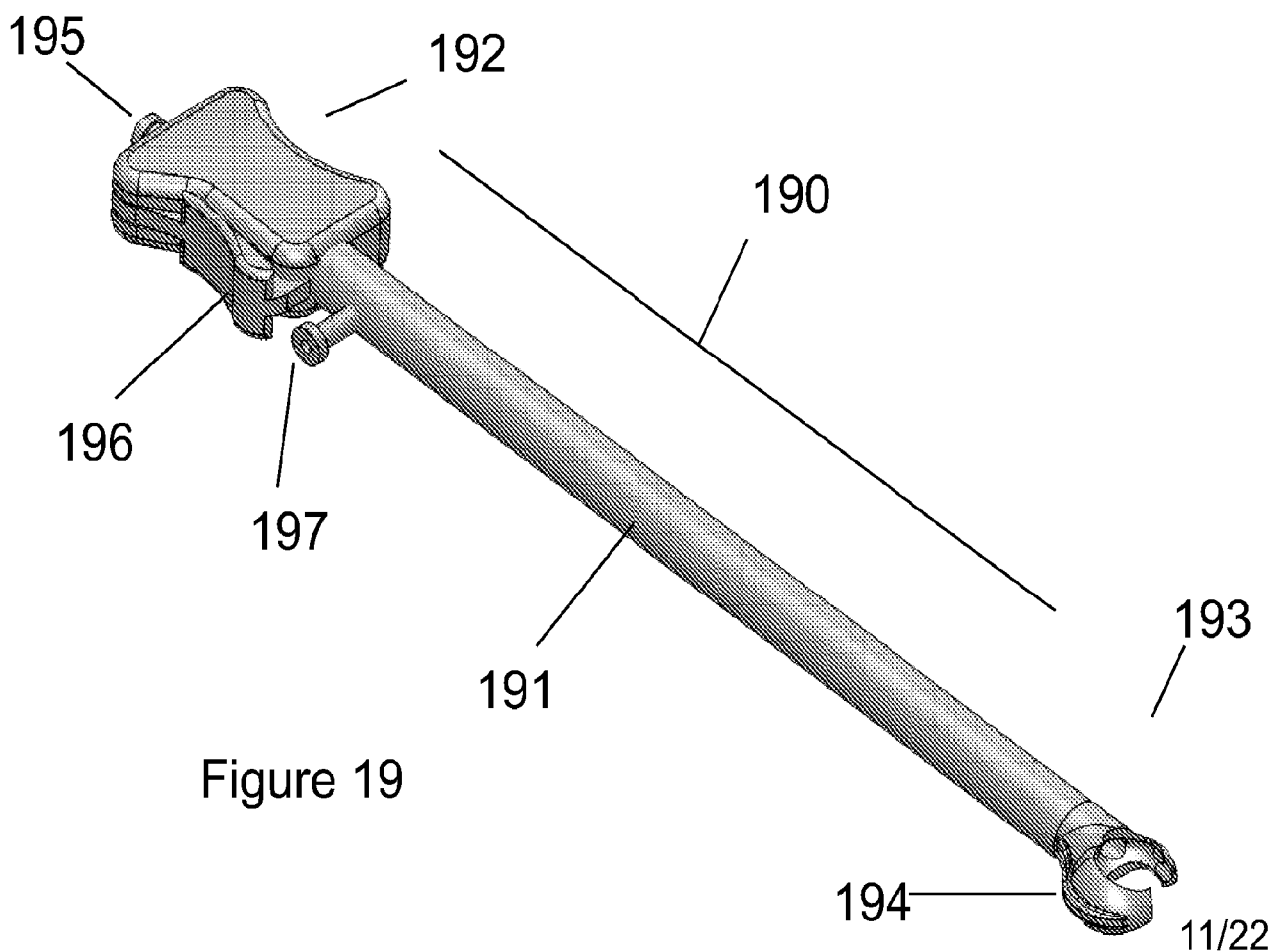


Figure 19

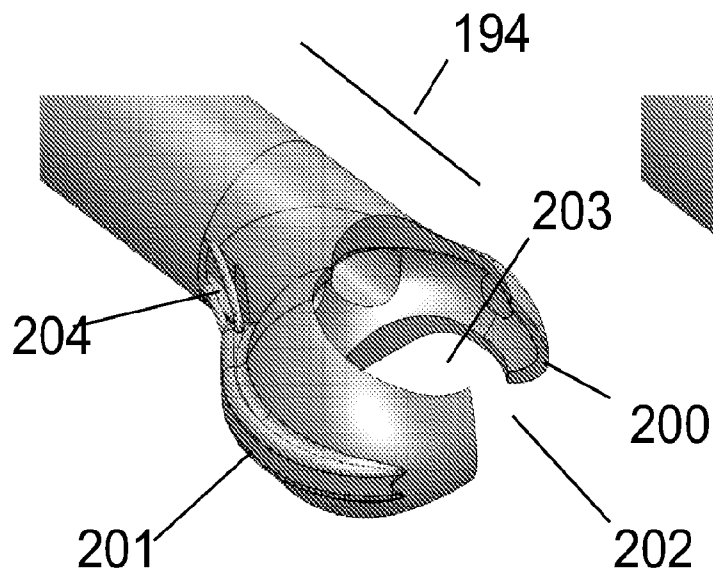


Figure 20a

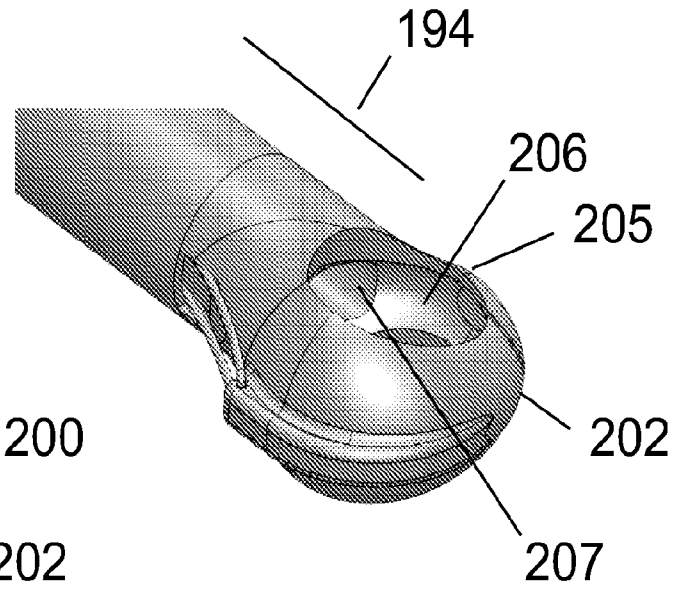


Figure 20b

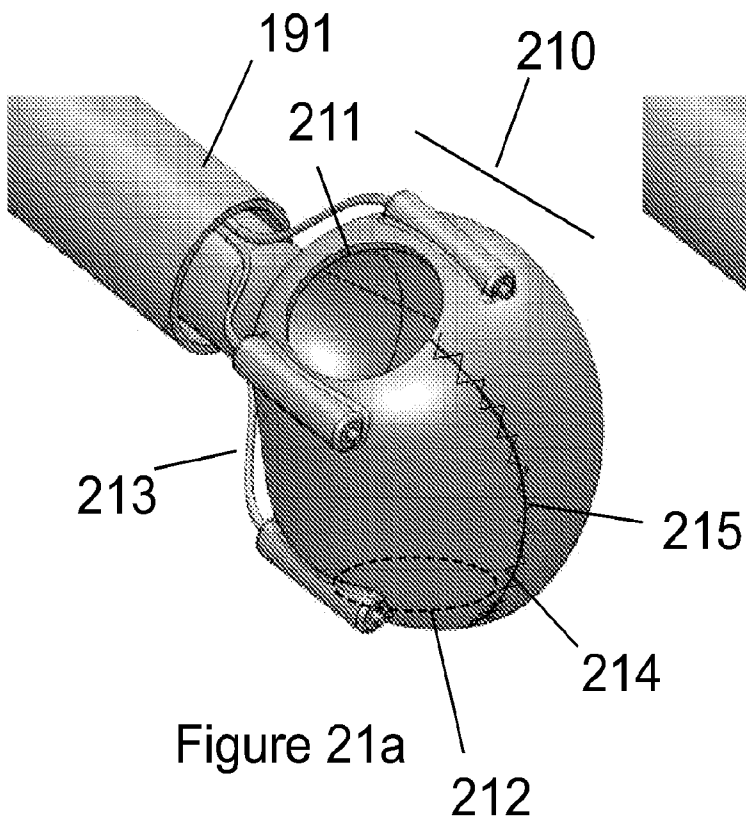


Figure 21a

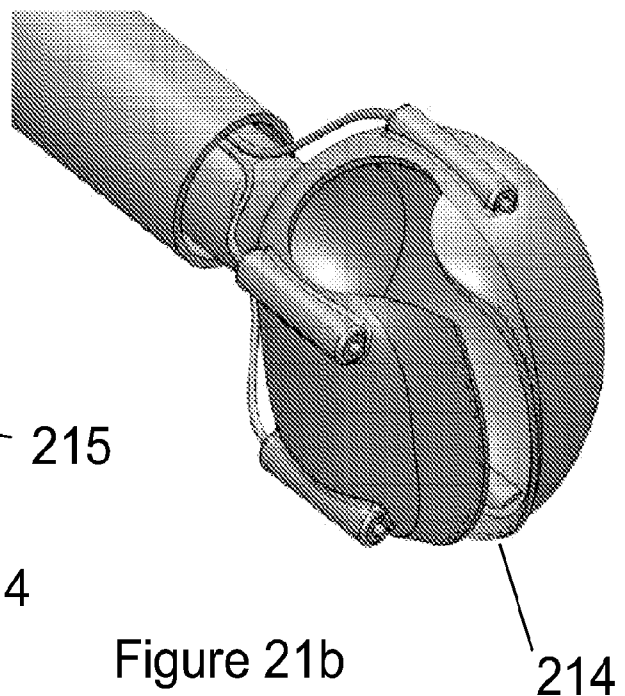


Figure 21b

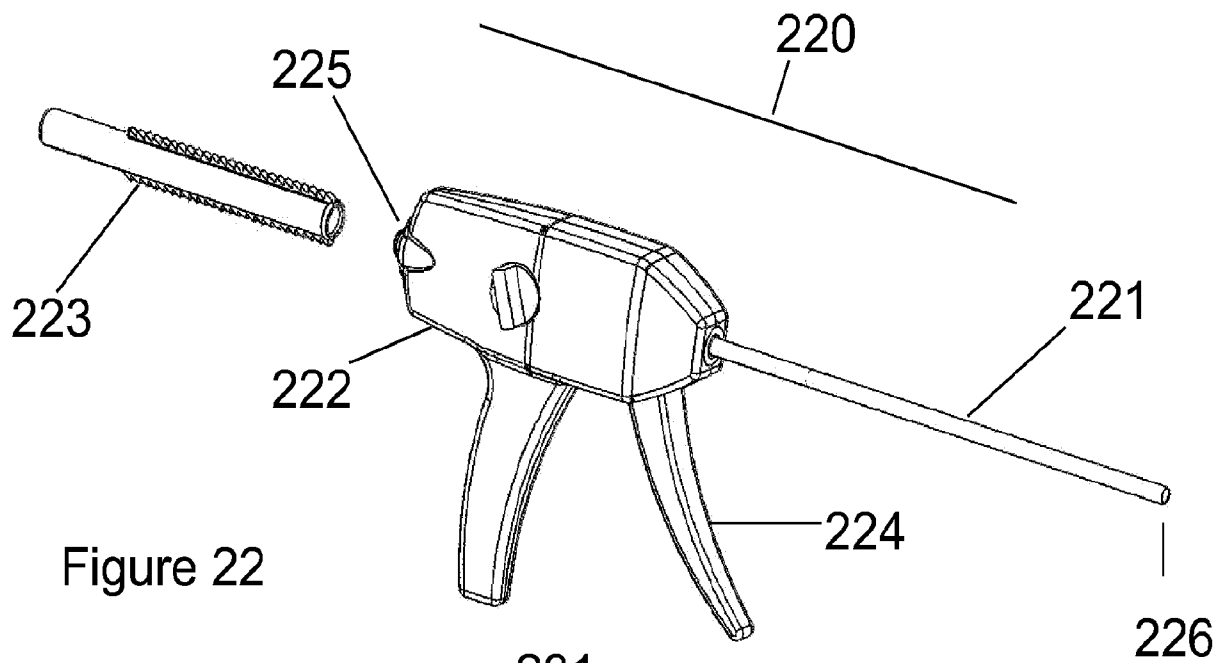


Figure 22

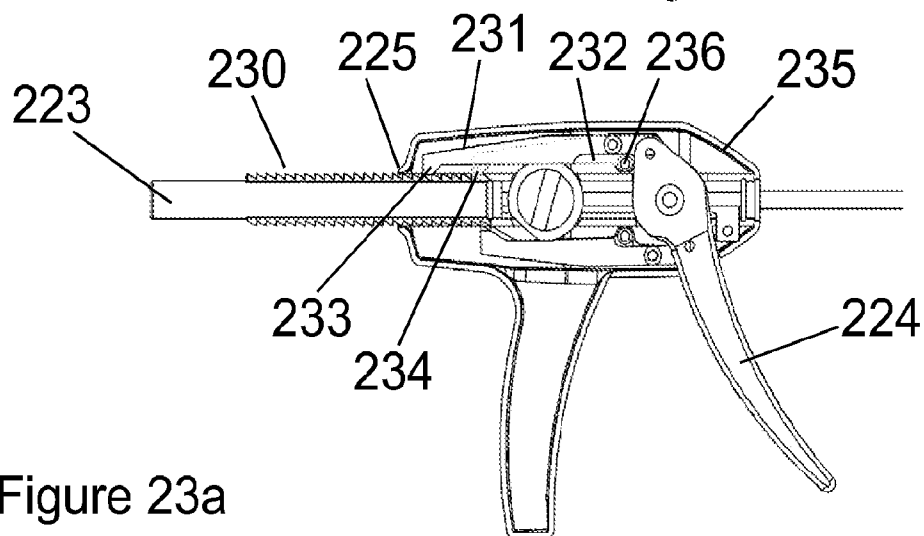


Figure 23a

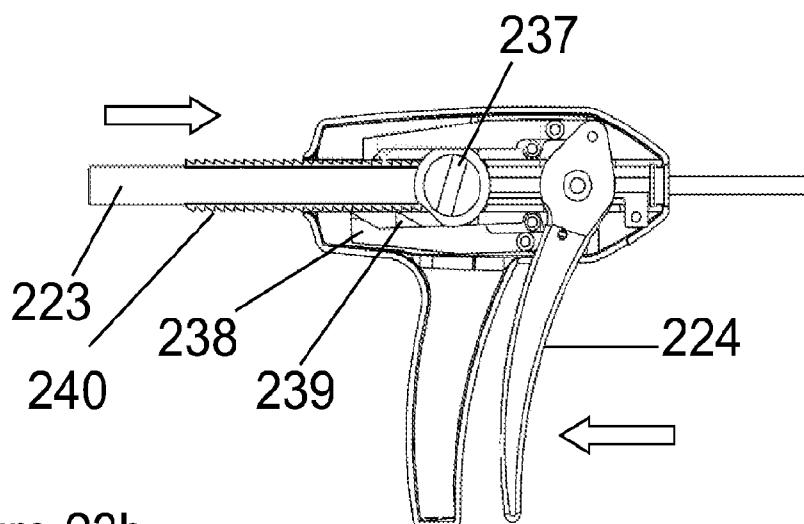


Figure 23b

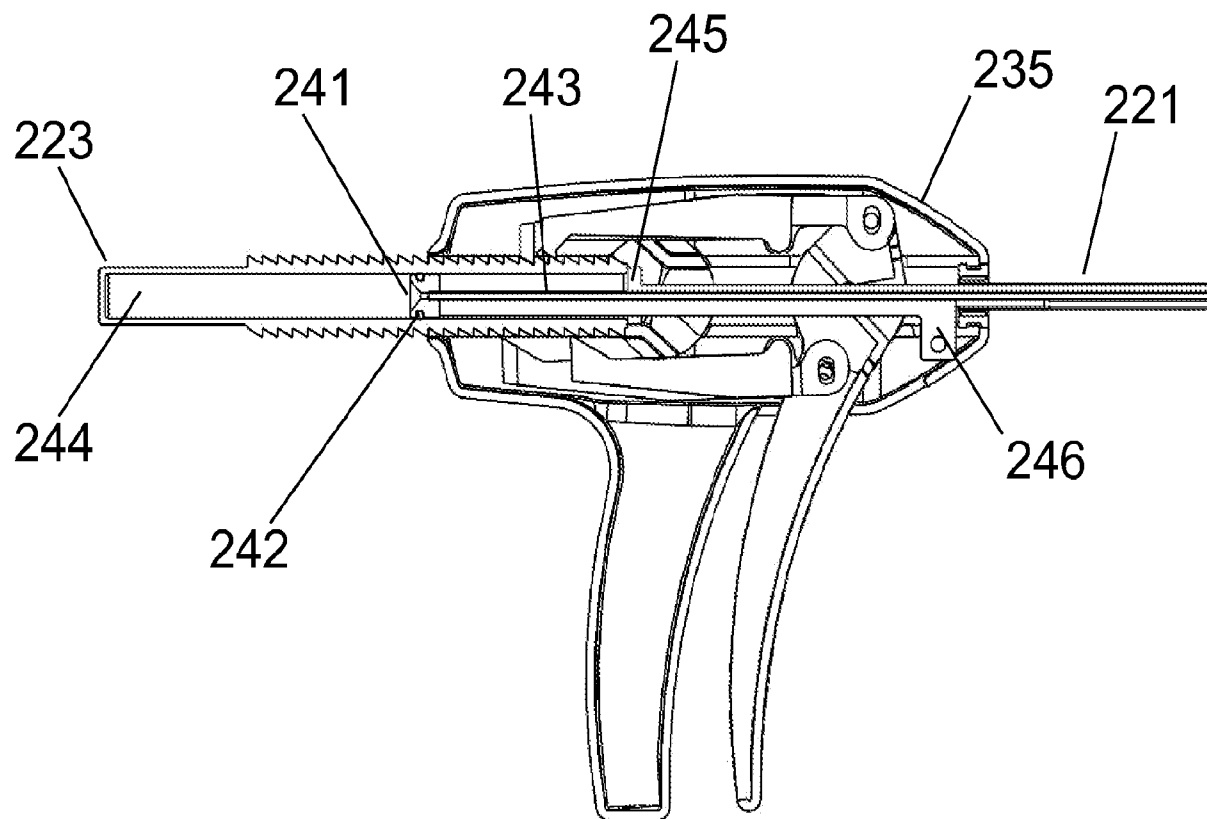
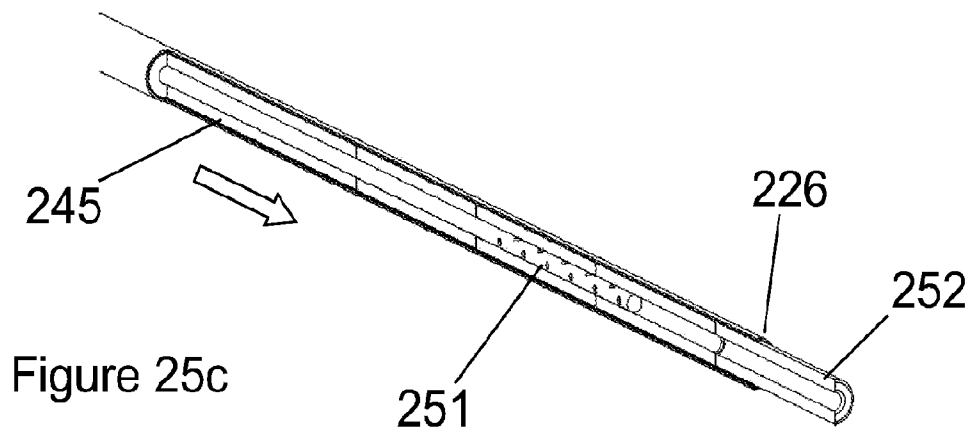
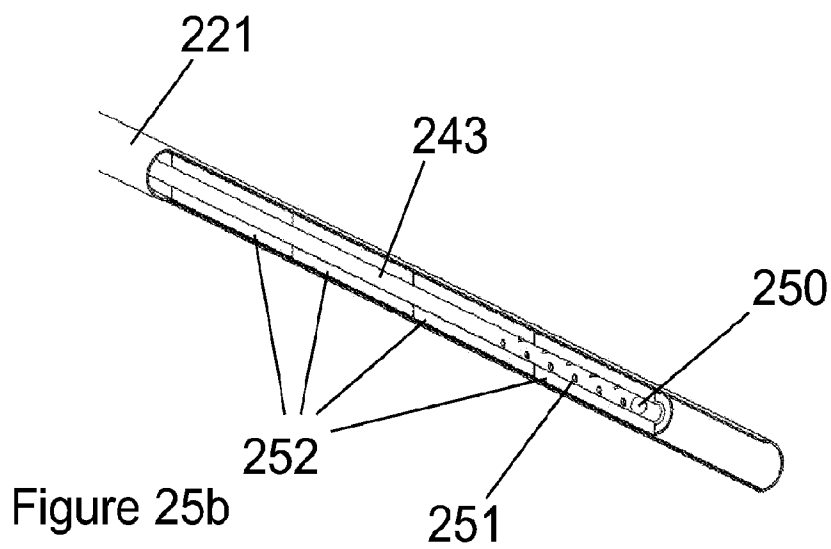
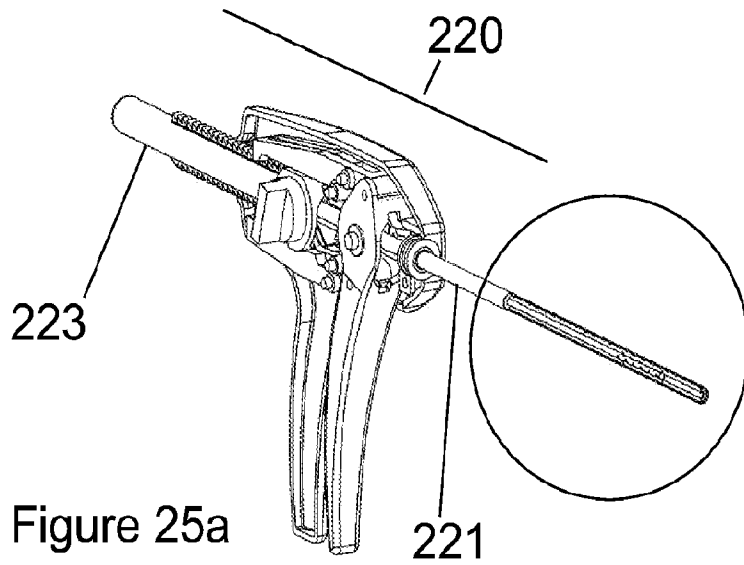


Figure 24



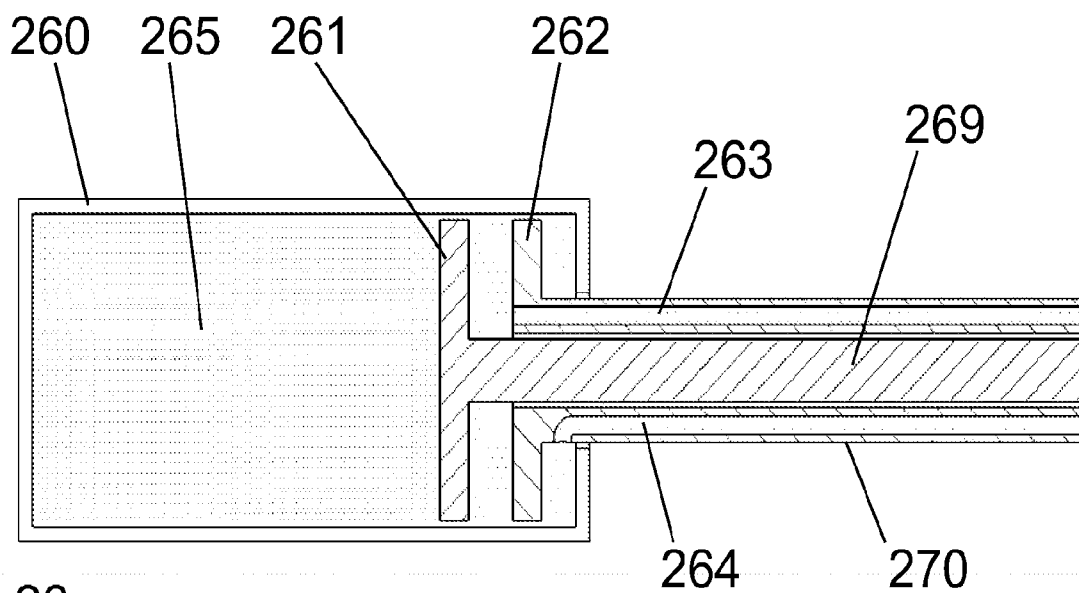


Figure 26a

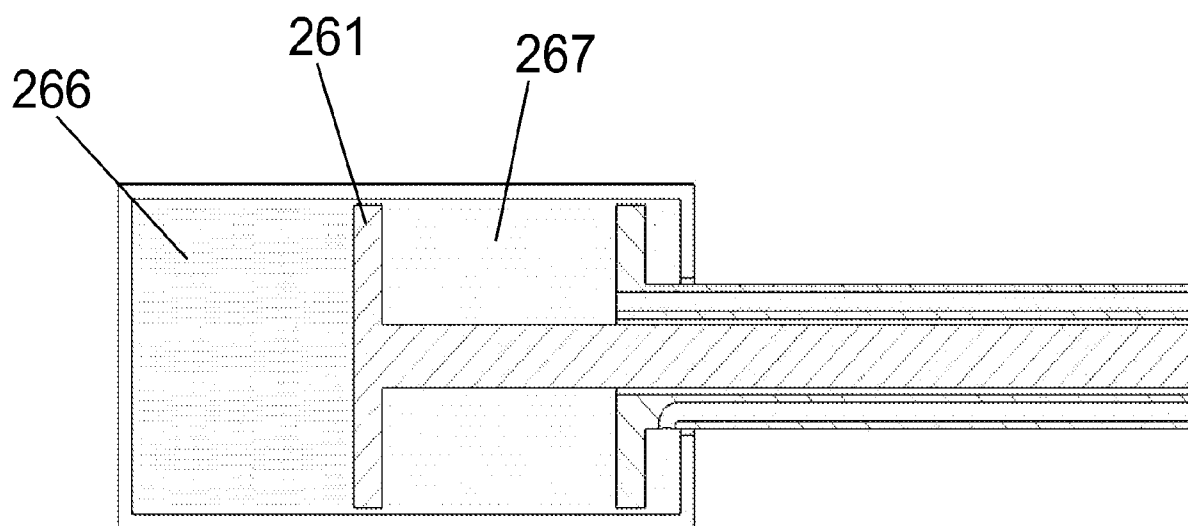


Figure 26b

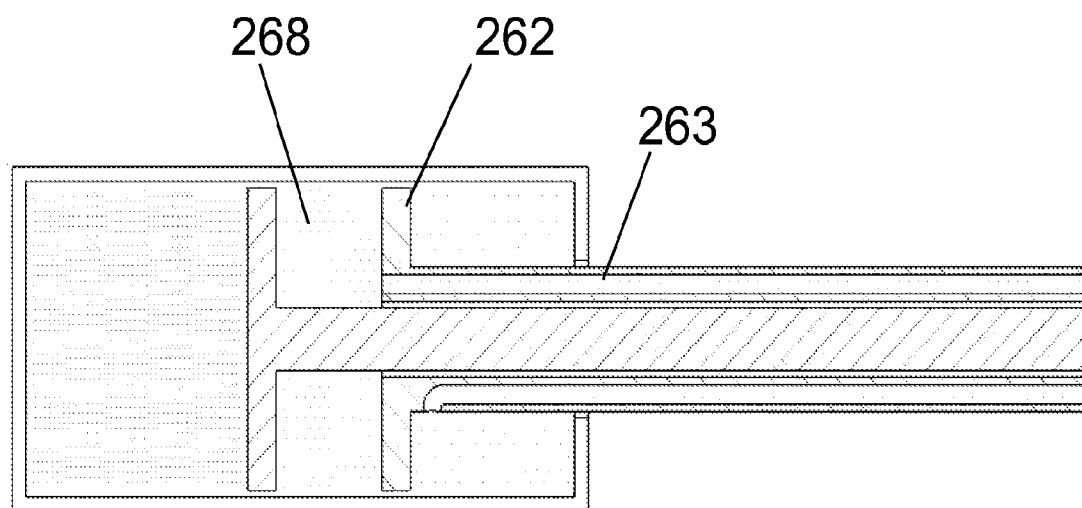


Figure 26c

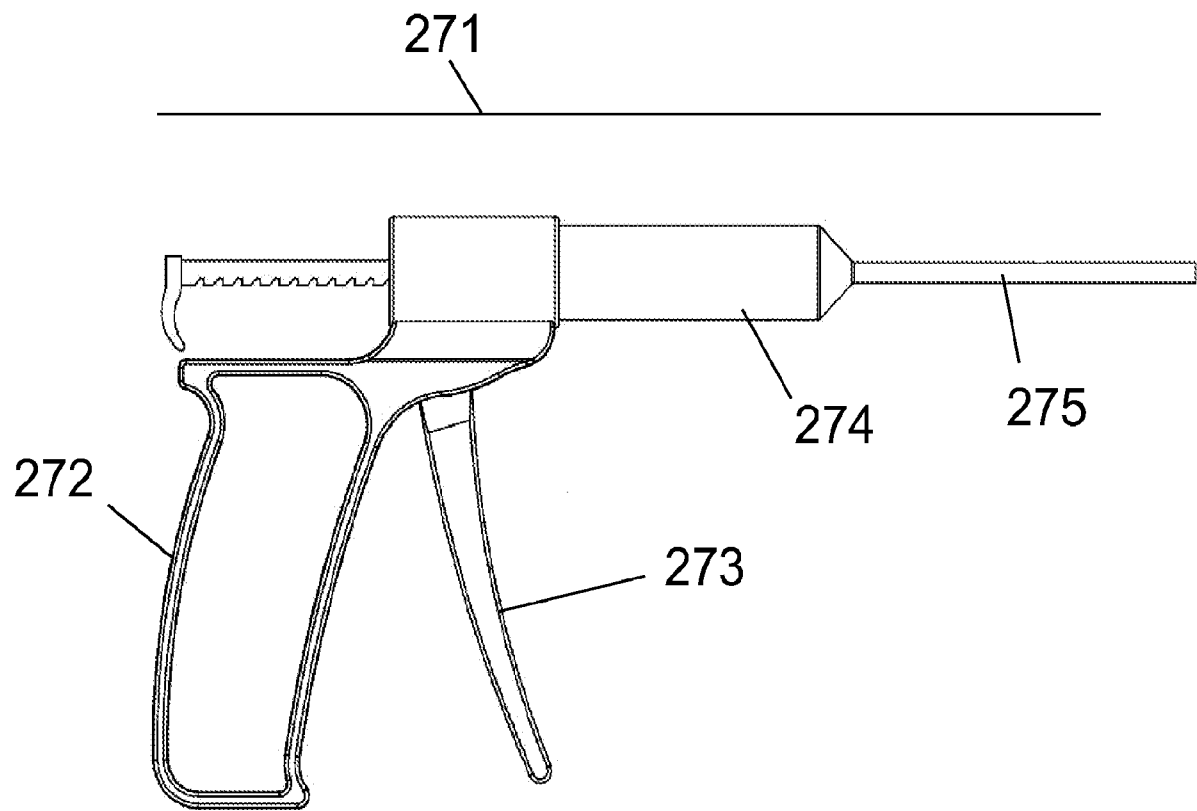


Figure 27a

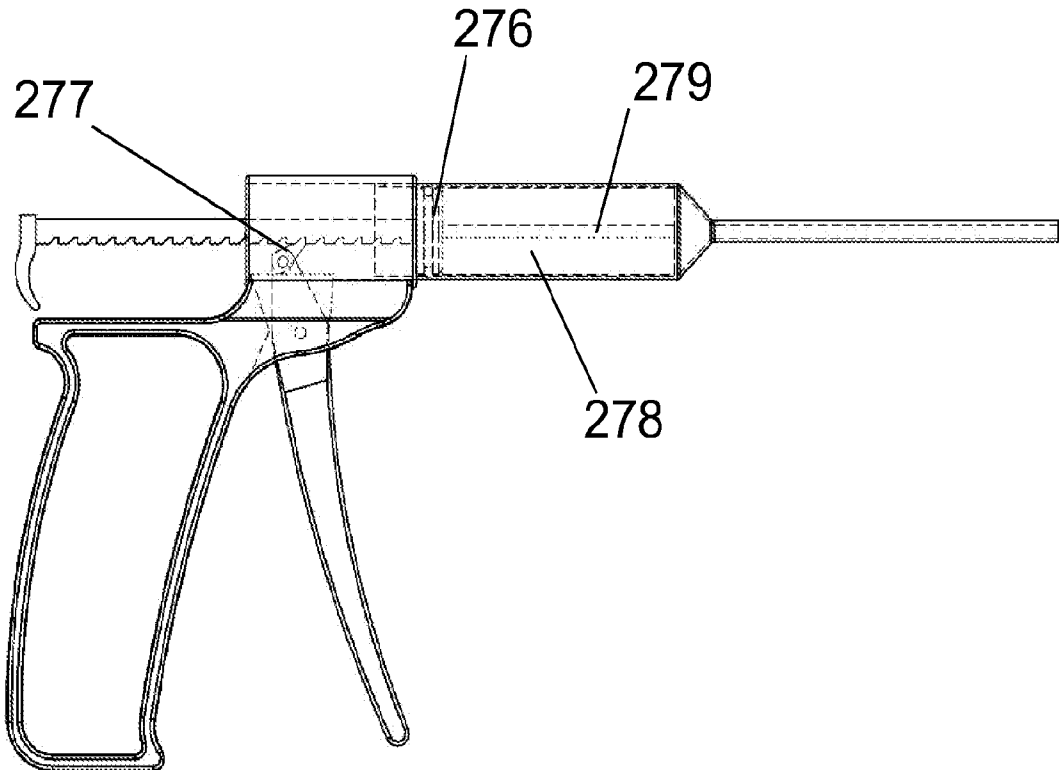
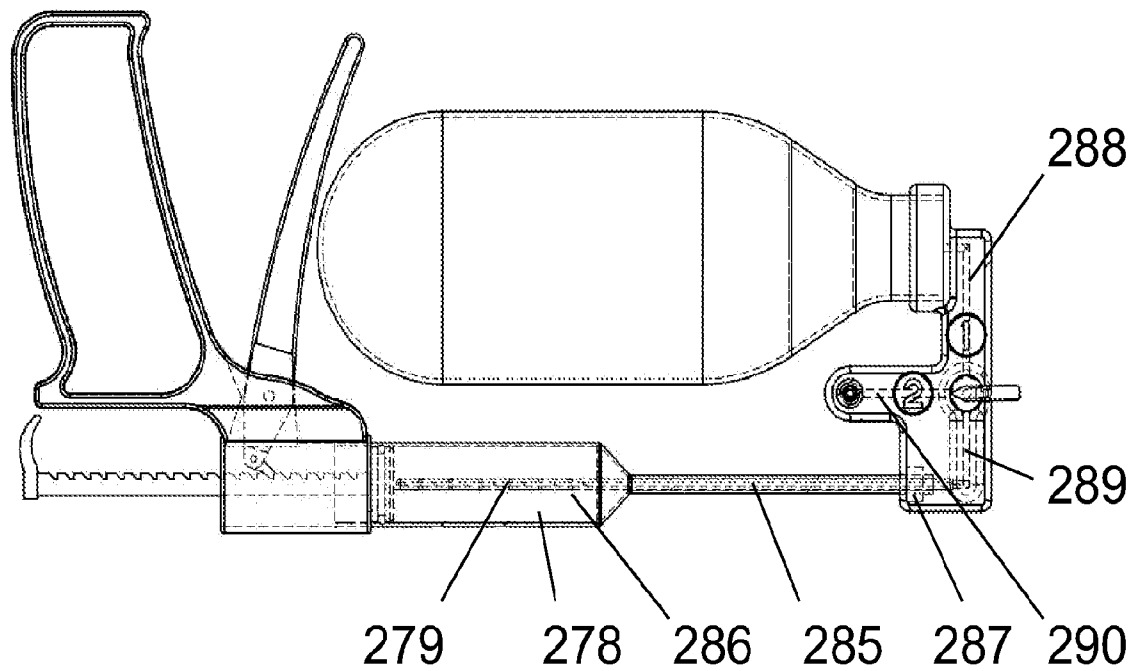
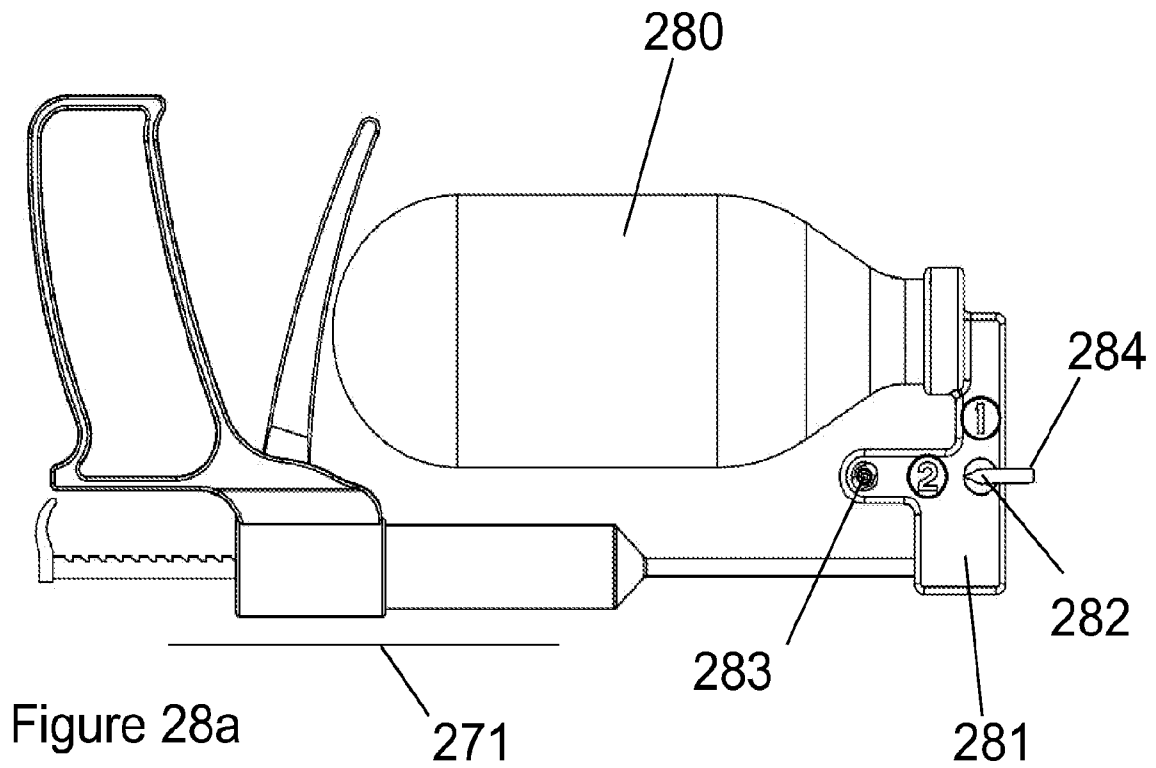
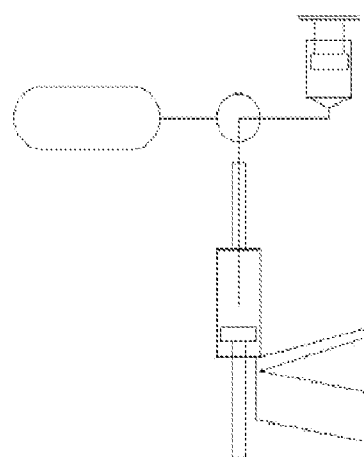
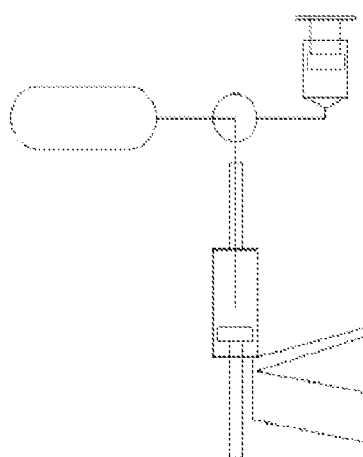
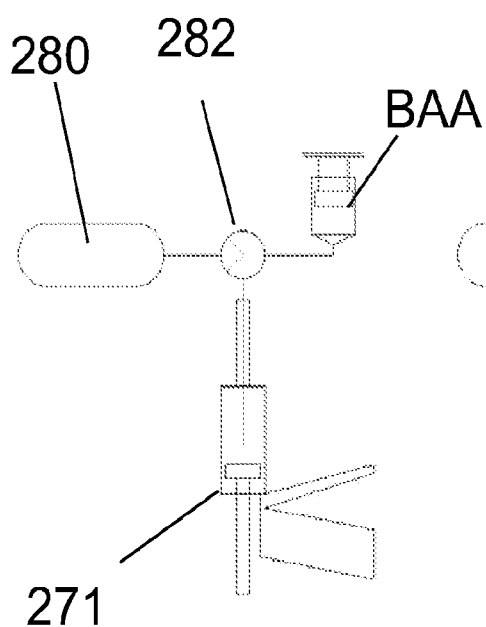
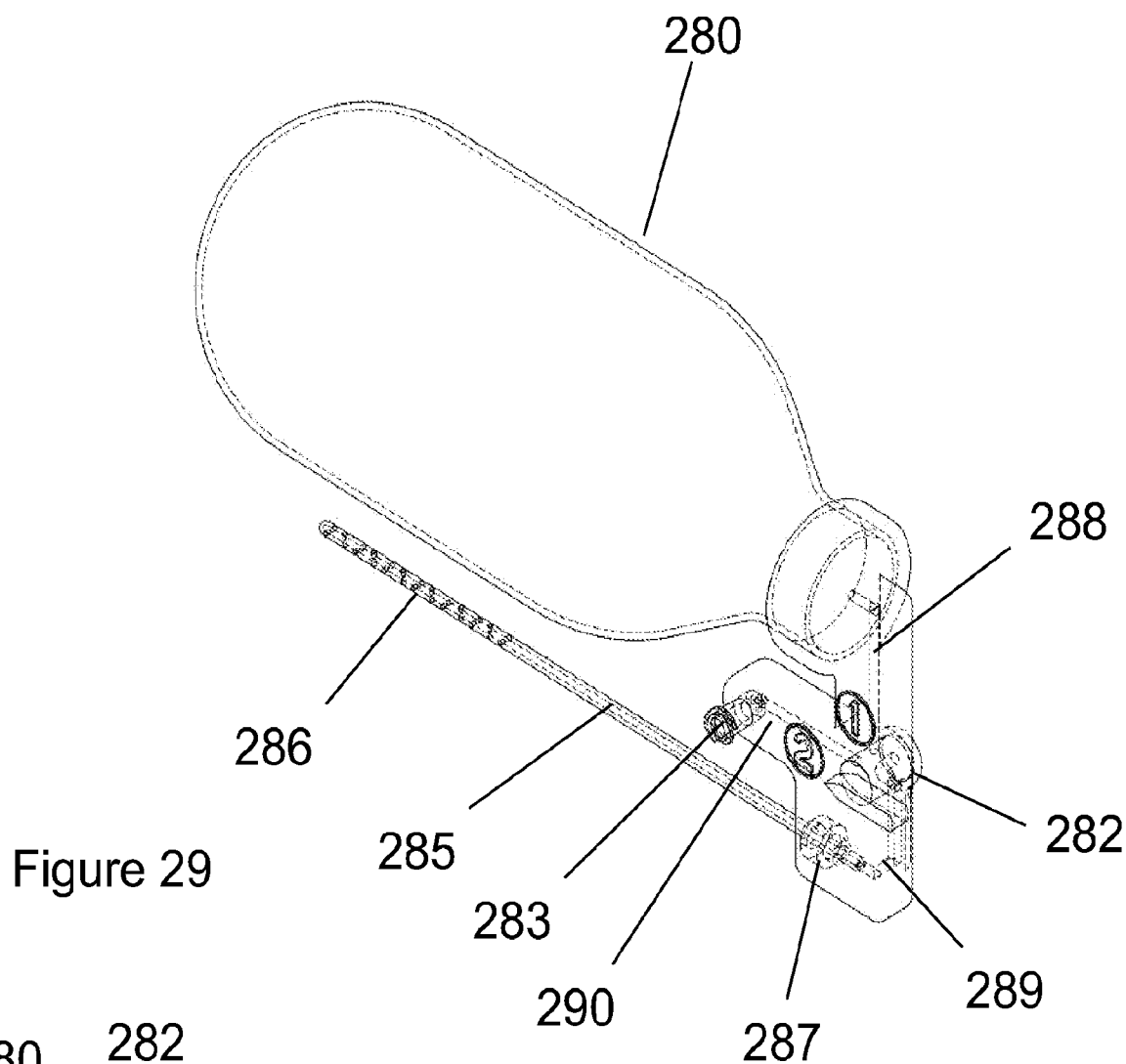


Figure 27b





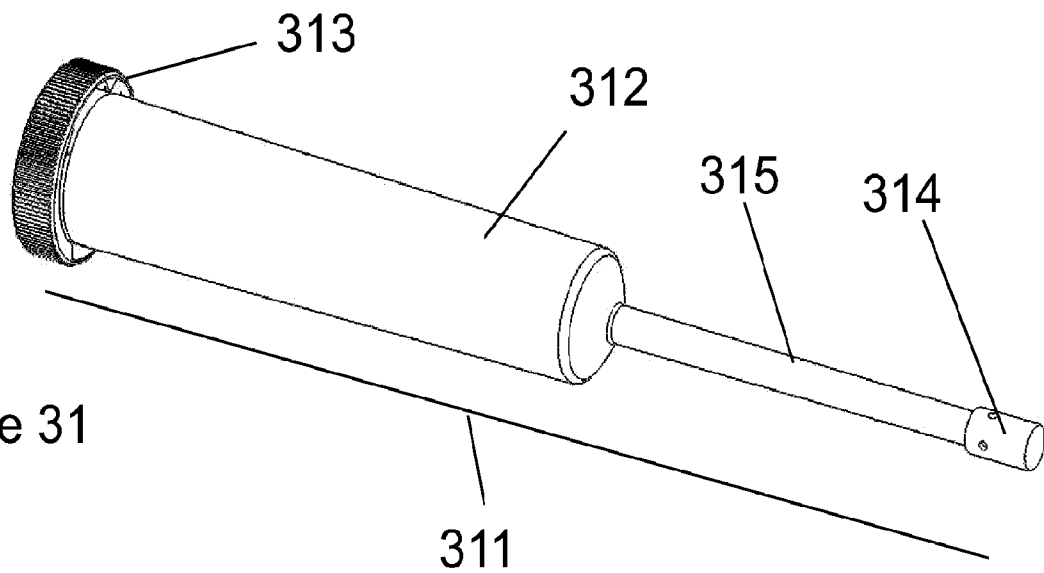


Figure 31

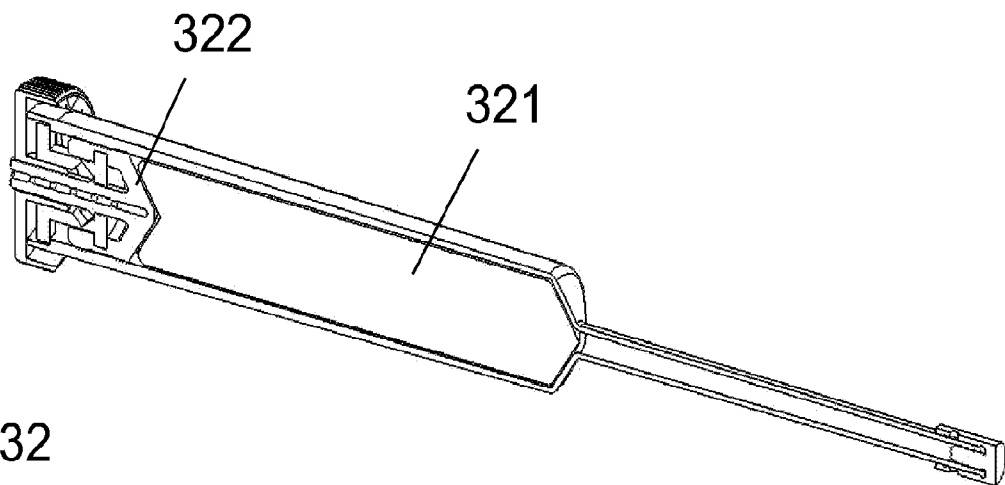


Figure 32

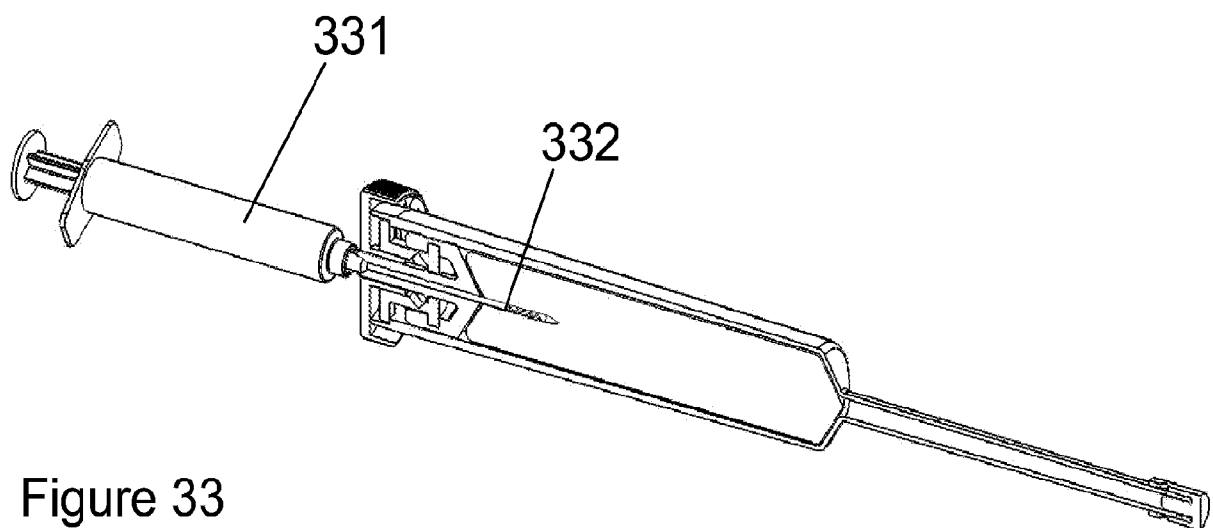


Figure 33

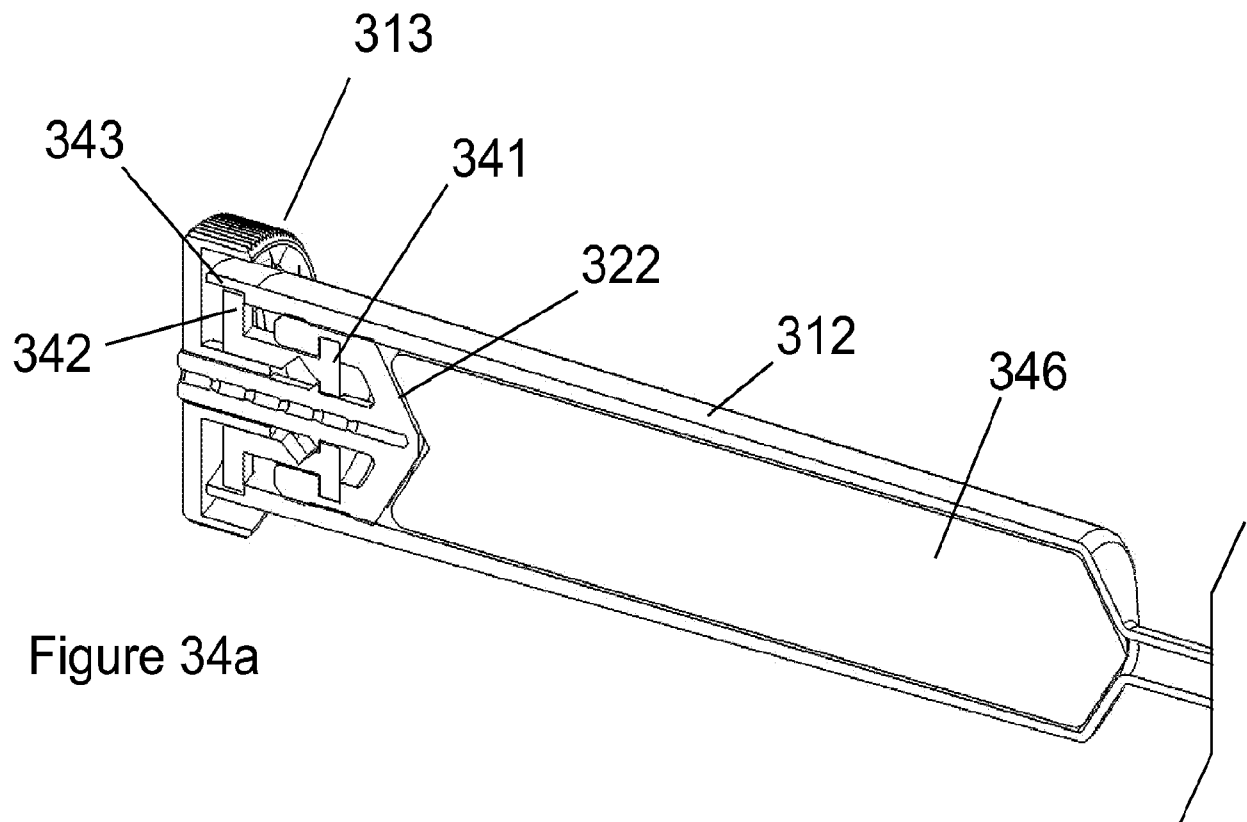


Figure 34a

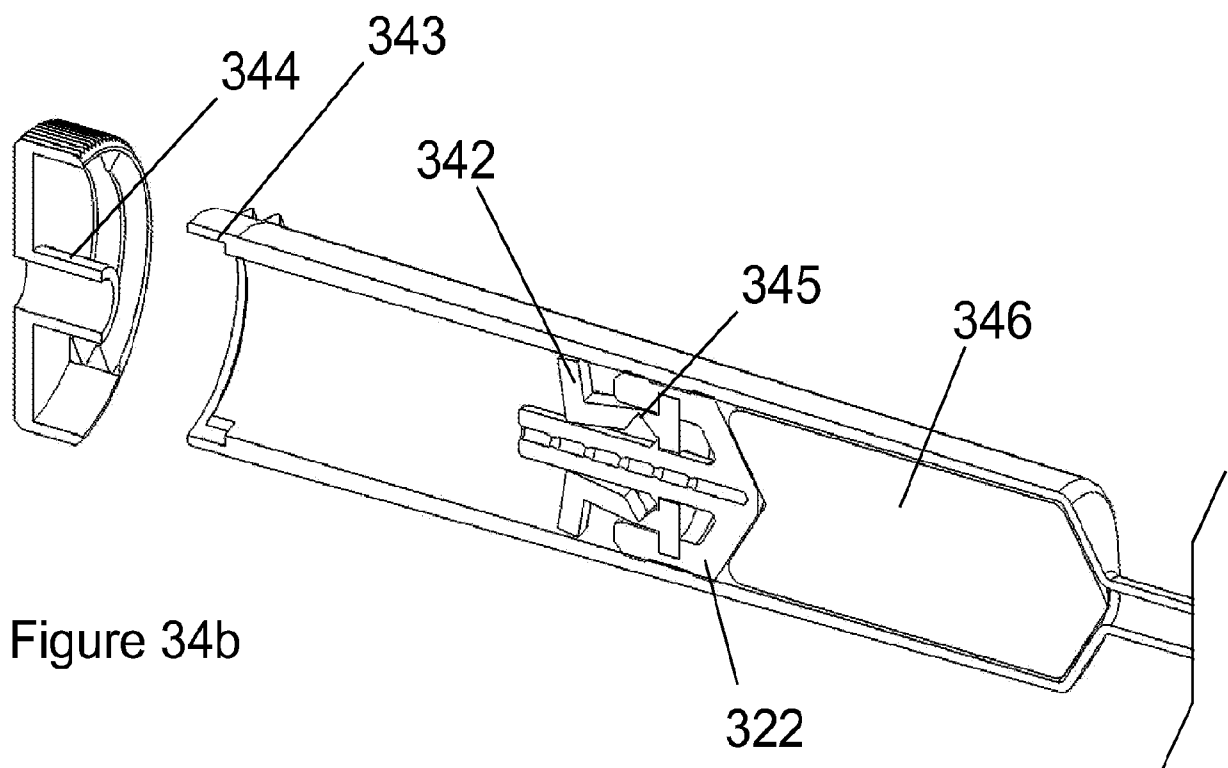
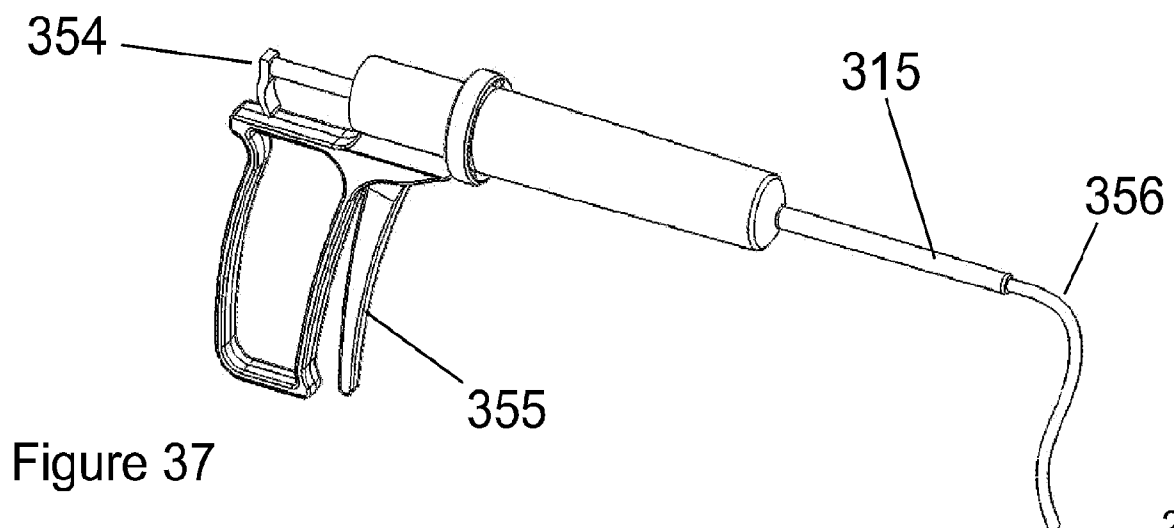
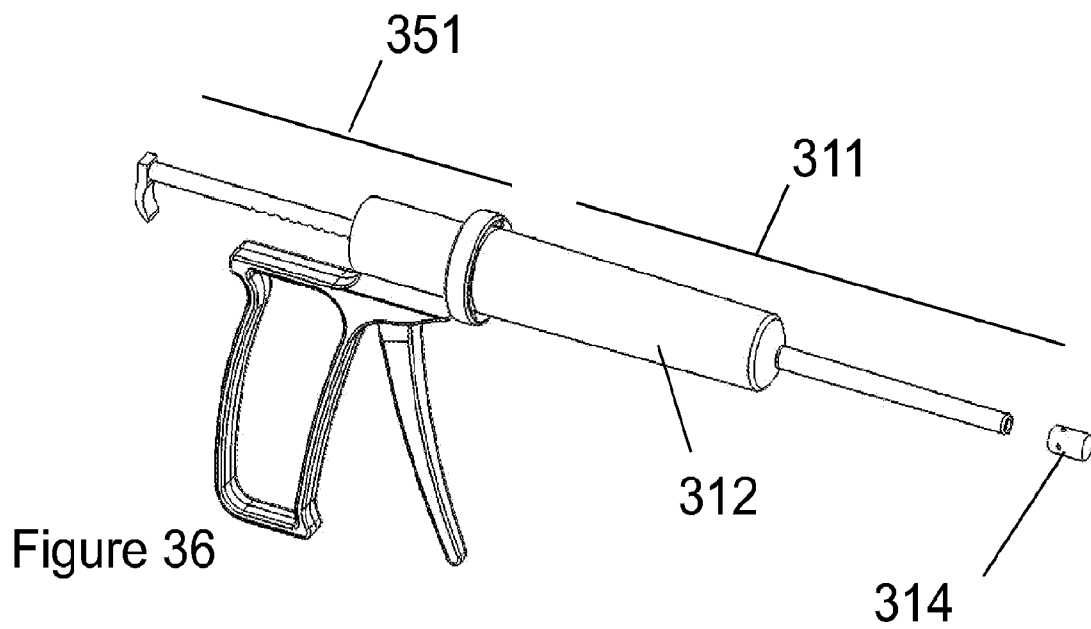
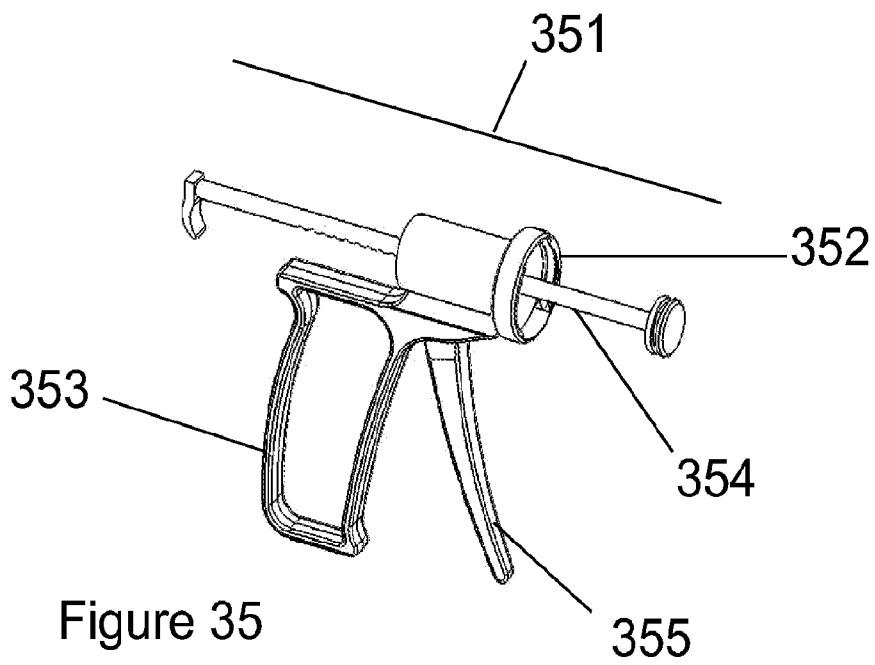


Figure 34b



## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2009/067380

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61B 17/11 (2010.01)

USPC - 623/13.18

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(8) - A61B 17/11, 17/56; A61F 2/08; A61L 27/54, 27/58; A61M 37/00 (2010.01)

USPC - 606/138, 139, 300; 623/11.11, 13.11, 13.12, 13.17, 13.18, 23.75, 23.76

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)

PatBase

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category*     | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No.                |
|---------------|------------------------------------------------------------------------------------|--------------------------------------|
| X<br>---<br>Y | WO 2007/087353 A2 (MURRAY) 02 August 2007 (02.08.2007) entire document             | 1-4, 7, 8, 10, 13, 14, 17, 20, 22-25 |
| X<br>---<br>Y | US 5,531,683 A (KRIESEL et al) 02 July 1996 (02.07.1996) entire document           | 5, 6, 9, 11, 12, 15, 16, 18, 19, 21  |
| X<br>---<br>Y | US 5,531,683 A (KRIESEL et al) 02 July 1996 (02.07.1996) entire document           | 26, 39                               |
| X<br>---<br>Y | US 5,531,683 A (KRIESEL et al) 02 July 1996 (02.07.1996) entire document           | 11, 12, 18, 19                       |
| X<br>---<br>Y | US 6,143,029 A (RIPPSTEIN) 07 November 2000 (07.11.2000) entire document           | 27                                   |
| X<br>---<br>Y | US 6,143,029 A (RIPPSTEIN) 07 November 2000 (07.11.2000) entire document           | 27                                   |
| X<br>---<br>Y | WO 00/35512 A2 (GENOTHERAPEUTICS INC) 22 June 2000 (22.06.2000) entire document    | 5, 6, 12, 21                         |
| X<br>---<br>Y | US 2004/0267362 A1 (HWANG et al) 30 December 2004 (30.12.2004) entire document     | 9                                    |
| X<br>---<br>Y | US 2004/0267362 A1 (HWANG et al) 30 December 2004 (30.12.2004) entire document     | 9                                    |
| X<br>---<br>Y | US 2005/0119613 A1 (MOENNING et al) 02 June 2005 (02.06.2005) entire document      | 15, 16                               |
| X<br>---<br>Y | US 5,707,377 A (KELLER et al) 13 January 1998 (13.01.1998) entire document         | 29-32                                |
| X<br>---<br>Y | US 5,707,377 A (KELLER et al) 13 January 1998 (13.01.1998) entire document         | 29-32                                |
| X<br>---<br>Y | US 2004/0116892 A1 (BURROUGHS et al) 17 June 2004 (17.06.2004) entire document     | 29-32                                |
| X<br>---<br>Y | US 2004/0116892 A1 (BURROUGHS et al) 17 June 2004 (17.06.2004) entire document     | 29-32                                |
| X<br>---<br>Y | US 2002/0198545 A1 (HESS et al) 26 December 2002 (26.12.2002) entire document      | 28                                   |
| X<br>---<br>Y | US 2002/0198545 A1 (HESS et al) 26 December 2002 (26.12.2002) entire document      | 28                                   |
| X<br>---<br>Y | US 5,571,181 A (LI) 05 November 1996 (05.11.1996) entire document                  | 28, 40-42                            |
| X<br>---<br>Y | US 5,571,181 A (LI) 05 November 1996 (05.11.1996) entire document                  | 28, 40-42                            |

☐ Further documents are listed in the continuation of Box C.

\* 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

"&amp;" document member of the same patent family

Date of the actual completion of the international search

02 April 2010

Date of mailing of the international search report

06 MAY 2010

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents  
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-3201

Authorized officer:

Blaine R. Copenheaver

PCT Helpdesk: 571-272-4300

PCT OSP: 571-272-7774

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2009/067380

| C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT |                                                                                    |                       |
|-------------------------------------------------------|------------------------------------------------------------------------------------|-----------------------|
| Category*                                             | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| A                                                     | US 5,266,075 A (CLARK et al) 30 November 1993 (30.11.1993) entire document         | 28                    |
| A                                                     | US 6,387,977 B1 (SAWHNEY et al) 14 May 2002 (14.05.2002) entire document           | 33-38, 40-42          |

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2009/067380

## 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.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I, claims 1-23, 27, and 29-32 are drawn to a therapeutic capsule device.

Group II, claims 24-26, 28, and 33-42 are drawn to an activation device.

The inventions listed in Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The special technical features of Group I, a therapeutic capsule device including a containment structure, are not present in Group II; and the special technical features of Group II, an activation device including a collagen matrix and pressure chamber, are not present in Group I.

Since none of the special technical features of the Group I and II inventions are found in more than one of the inventions, unity is lacking.

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.