

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
8 January 2009 (08.01.2009)

PCT

(10) International Publication Number
WO 2009/006008 A1

- (51) International Patent Classification:
C12N 13/00 (2006.01)
- (21) International Application Number:
PCT/US2008/067124
- (22) International Filing Date: 16 June 2008 (16.06.2008)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
11/771,945 29 June 2007 (29.06.2007) US
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- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.
- (84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL,

[Continued on next page]

(54) Title: DEVICES AND METHODS FOR SELECTIVELY LYSING CELLS

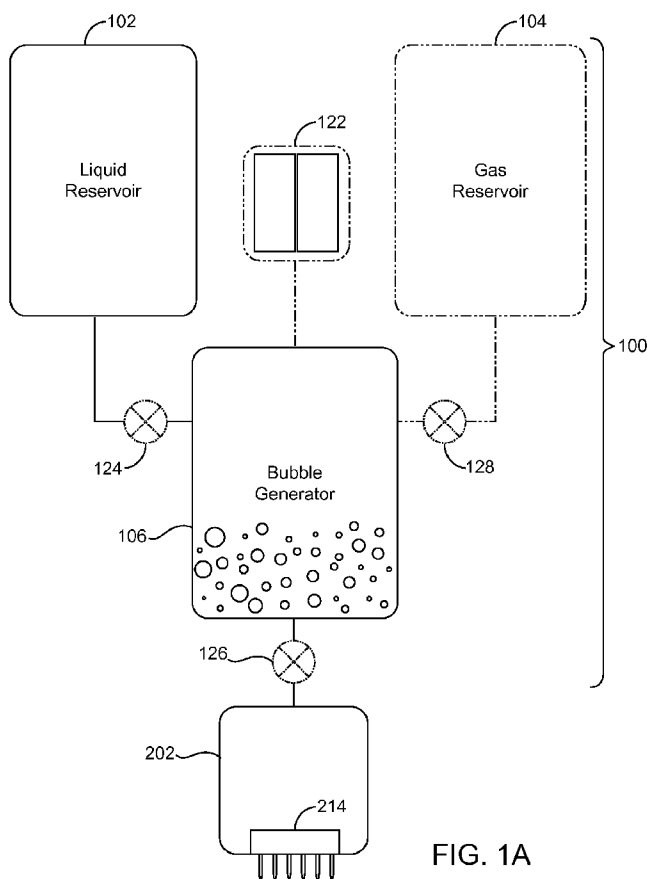


FIG. 1A

(57) Abstract: A system comprising: a container containing a measured amount of a solution including at least one of a vasoconstrictor, a surfactant, and an anesthetic, the solution comprising a liquid and at least one of a gas and a fluid; a needle array in fluid connection with the container, the needle array including at least one needle.

WO 2009/006008 A1



NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG,
CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

DEVICES AND METHODS FOR SELECTIVELY LYSING CELLS

Claim for Priority/ Reference to Co pending Applications.

This application claims priority to U.S. Utility Patent Application Serial Number 11/515,634 filed September 5, 2006, U.S. Utility Patent Application Serial Number
5 11/334,794 filed January 17, 2006, U.S. Utility Patent Application Serial Number 11/334,805 filed January 17, 2006, and U.S. Utility Patent Application Serial Number 11/292,950 filed December 2, 2005, the entirety of which are incorporated herein by reference.

Field of the Invention:

10 The present invention relates to a microbubble generation device and a system for selectively lysing cells by cavitating microbubbles.

Background of the Invention:

Gynoid lipodystrophy is a localized metabolic disorder of the subcutaneous tissue which leads to an alteration in the topography of the cutaneous surface (skin), or a
15 dimpling effect caused by increased fluid retention and/or proliferation of adipose tissue in certain subdermal regions. This condition, commonly known as cellulite, affects over 90% of post-pubescent women, and some men. Cellulite commonly appears on the hips, buttocks and legs, but is not necessarily caused by being overweight, as is a common perception. Cellulite is formed in the subcutaneous level of tissue below the epidermis and
20 dermis layers. In this region, fat cells are arranged in chambers surrounded by bands of connective tissue called septae. As water is retained, fat cells held within the perimeters defined by these fibrous septae expand and stretch the septae and surrounding connective tissue. Furthermore, adipocyte expansion from weight gain may also stretch the septae. Eventually this connective tissue contracts and hardens (scleroses) holding the skin at a
25 non-flexible length, while the chambers between the septae continue to expand with weight gain, or water gain. This results in areas of the skin being held down while other sections bulge outward, resulting in the lumpy, "orange peel" or "cottage-cheese" appearance on the skin surface.

Even though obesity is not considered to be a root cause of cellulite, it can certainly
30 worsen the dimpled appearance of a cellulitic region due to the increased number of fat cells in the region. Traditional fat extraction techniques such as liposuction that target deep fat and larger regions of the anatomy, can sometimes worsen the appearance of cellulite since the subdermal fat pockets remain and are accentuated by the loss of underlying bulk

(deep fat) in the region. Many times liposuction is performed and patients still seek therapy for remaining skin irregularities, such as cellulite.

A variety of approaches for treatment of skin irregularities such as cellulite and removal of unwanted adipose tissue have been proposed. For example, methods and devices that provide mechanical massage to the affected area, through either a combination
5 of suction and massage or suction, massage and application of energy, in addition to application of various topical agents are currently available. Developed in the 1950's, mesotherapy is the injection of various treatment solutions through the skin that has been widely used in Europe for conditions ranging from sports injuries to chronic pain, to
10 cosmetic procedures to treat wrinkles and cellulite. The treatment consists of the injection or transfer of various agents through the skin to provide increased circulation and the potential for fat oxidation, such as aminophylline, hyaluronic acid, novocaine, plant extracts and other vitamins. The treatment entitled Acthyderm (Turnwood International, Ontario, Canada) employs a roller system that electroporates the stratum corneum to open
15 small channels in the dermis, followed by the application of various mesotherapy agents, such as vitamins, antifibrotics, lypolitics, anti-inflammatories and the like.

Massage techniques that improve lymphatic drainage were tried as early as the 1930's. Mechanical massage devices, or Pressotherapy, have also been developed such as the "Endermologie" device (LPG Systems, France), the "Synergie" device (Dynatronics,
20 Salt Lake City, Utah) and the "Silklight" device (Lumenis, Tel Aviv, Israel), all utilizing subdermal massage via vacuum and mechanical rollers. Other approaches have included a variety of energy sources, such as Cynosure's "TriActive" device (Cynosure, Westford, Mass.) utilizing a pulsed semiconductor laser in addition to mechanical massage, and the "Cellulux" device (Palomar Medical, Burlington, Mass.) which emits infrared light
25 through a cooled chiller to target subcutaneous adipose tissue. The "VelaSmooth" system (Syneron, Inc., Yokneam Illit, Israel) employs bipolar radiofrequency energy in conjunction with suction to increase metabolism in adipose tissue, and the "Thermacool" device (Thermage, Inc., Hayward, Calif.) utilizes radiofrequency energy to shrink the subdermal fibrous septae to treat wrinkles and other skin defects. Other energy based
30 therapies such as electrolipophoresis, using several pairs of needles to apply a low frequency interstitial electromagnetic field to aid circulatory drainage have also been developed. Similarly, non-invasive ultrasound is used in the "Dermosonic" device (Symedex Medical, Minneapolis, Minn.) to promote reabsorption and drainage of retained fluids and toxins.

Another approach to the treatment of skin irregularities such as scarring and dimpling is a technique called subcision. This technique involves the insertion of a relatively large gauge needle subdermally in the region of dimpling or scarring, and then mechanically manipulating the needle below the skin to break up the fibrous septae in the subdermal region. In at least one known method of subcision, a local anesthetic is injected into the targeted region, and an 18 gauge needle is inserted 10-20 mm below the cutaneous surface. The needle is then directed parallel to the epidermis to create a dissection plane beneath the skin to essentially tear through, or "free up" the tightened septae causing the dimpling or scarring. Pressure is then applied to control bleeding acutely, and then by the use of compressive clothing following the procedure. While clinically effective in some patients, pain, bruising, bleeding and scarring can result. The known art also describes a laterally deployed cutting mechanism for subcision, and a technique employing an ultrasonically assisted subcision technique.

Certain other techniques known as liposuction, tumescent liposuction, lypolysis and the like, target adipose tissue in the subdermal and deep fat regions of the body. These techniques may include also removing the fat cells once they are disrupted, or leaving them to be resorbed by the body's immune/lymphatic system. Traditional liposuction includes the use of a surgical cannula placed at the site of the fat to be removed, and then the use of an infusion of fluids and mechanical motion of the cannula to break up the fatty tissue, and suction to "vacuum" the disrupted fatty tissue directly out of the patient.

The "Lysonix" system (Mentor Corporation, Santa Barbara, Calif.) utilizes an ultrasonic transducer on the handpiece of the suction cannula to assist in tissue disruption (by cavitation of the tissue at the targeted site). Liposonix (Bothell, Wash.) and Ultrashape (TelAviv, Israel) employ the use of focused ultrasound to destroy adipose tissue noninvasively. In addition, cryogenic cooling has been proposed for destroying adipose tissue. A variation on the traditional liposuction technique known as tumescent liposuction was introduced in 1985 and is currently considered by some to be the standard of care in the United States. It involves the infusion of tumescent fluids to the targeted region prior to mechanical disruption and removal by the suction cannula. The fluids may help to ease the pain of the mechanical disruption, while also swelling the tissues making them more susceptible to mechanical removal. Various combinations of fluids may be employed in the tumescent solution including a local anesthetic such as lidocaine, a vasoconstrictive agent such as epinephrine, saline, potassium and the like. The benefits of such an approach are detailed in the articles, "Laboratory and Histopathologic Comparative Study of Internal

Ultrasound-Assisted Lipoplasty and Tumescent Lipoplasty" Plastic and Reconstructive Surgery, Sep. 15, (2002) 110:4, 1158-1164, and "When One Liter Does Not Equal 1000 Milliliters: Implications for the Tumescent Technique" Dermatol. Surg. (2000) 26:1024-1028, the contents of which are expressly incorporated herein by reference in their entirety.

5 Various other approaches employing dermatologic creams, lotions, vitamins and herbal supplements have also been proposed to treat cellulite. Private spas and salons offer cellulite massage treatments that include body scrubs, pressure point massage, essential oils, and herbal products using extracts from plant species such as seaweed, horsetail and clematis and ivy have also been proposed. Although a multitude of therapies exist, most of
10 them do not provide a lasting effect on the skin irregularity, and for some, one therapy may cause the worsening of another (as in the case of liposuction causing scarring or a more pronounced appearance of cellulite). Yet other treatments for cellulite have negative side effects that limit their adoption. Most therapies require multiple treatments on an ongoing basis to maintain their effect at significant expense and with mixed results.

15 Medical ultrasound apparatus and methods are generally of two different types. One type of medical ultrasound wave generating device known in the art is that which provides high intensity focused ultrasound or high acoustic pressure ultrasound for tissue treatment, for example for tumor destruction. High intensity or high acoustic pressure ultrasound is capable of providing direct tissue destruction. High intensity or high acoustic
20 pressure ultrasound is most commonly focused at a point in order to concentrate the energy from the generated acoustic waves in a relatively small focus of tissue. However, another type of medical ultrasound is a lower intensity and less focused type of ultrasound that is used for diagnostic imaging and physical therapy applications. Low acoustic pressure ultrasound is commonly used, for example, for cardiac imaging and fetal imaging. Low
25 acoustic pressure ultrasound may be used for tissue warning, without tissue disruption, in physical therapy applications. Low acoustic pressure ultrasound, using power ranges for diagnostic imaging, generally will not cause any significant tissue disruption when used for limited periods of time in the absence of certain enhancing agents.

 Methods and apparatus of using high intensity focused ultrasound to disrupt
30 subcutaneous tissues directly has been described in the known art. Such techniques may utilize a high intensity ultrasound wave that is focused on a tissue within the body, thereby causing a localized destruction or injury to cells. The focusing of the high intensity ultrasound may be achieved utilizing, for example, a concave transducer or an acoustic lens. Use of high intensity focused ultrasound to disrupt fat, sometimes in combination

with removal of the fat by liposuction, has been described in the known prior art. Such use of high intensity focused ultrasound should be distinguished from the low acoustic pressure ultrasound.

In light of the foregoing, it would be desirable to provide methods and apparatus for treating skin irregularities such as cellulite and to provide a sustained aesthetic result to a body region, such as the face, neck, arms, legs, thighs, buttocks, breasts, stomach and other targeted regions which are minimally or non-invasive. It would also be desirable to provide methods and apparatus for treating skin irregularities that enhance prior techniques and make them less invasive and subject to fewer side effects.

Therefore, there has been recognized by those skilled in the art a need for an apparatus and method for the use of low intensity ultrasound to treat subcutaneous tissues. Use of low intensity ultrasound, in the power ranges of diagnostic ultrasound, would be safer to use, have fewer side effects, and could be used with less training. The present invention fulfills these needs and others.

SUMMARY OF THE INVENTION

Disclosed is a device for generating microbubbles in a gas and liquid mixture and injection device, which includes a housing defining a mixing chamber; means for mixing solution contained in the mixing chamber to generate microbubbles in the solution; and a needle array removably attached to the housing and in fluid connection with the mixing chamber, the needle array including at least one needle.

The mixing chamber may include a first mixing chamber in fluid communication with a second mixing chamber. Moreover, the mixing means may include means for expressing a solution of fluid and gas between the first and second mixing chambers to generate microbubbles in the solution.

The device may further include a fluid reservoir in fluid connection with at least one of the first and second mixing chambers; and a source of gas in fluid connection with at least one of the first and second mixing chambers. Optionally, the fluid reservoir and/or the mixing chamber(s) may be thermally insulated and/or include means for maintaining the fluid at a predetermined temperature. Still further, the source of gas may be room air, or may include air, oxygen, carbon dioxide, perfluoropropane or the like which may be maintained at greater than atmospheric pressure.

The solution expressing means may include first and second pistons mounted for reciprocation within the first and second mixing chambers.

Still further, the device may include means for reciprocating the first and second pistons to express fluid and gas between the first and second cylinders to create a microbubble solution. The reciprocating means may be a source of compressed air; and the first and second cylinders may be pneumatic cylinders.

5 The device may include a needle deployment mechanism operably connected to the needle array for deploying the at least one needle(s) between a retracted and an extended position. The needle array may include at least two needles and the needle deployment mechanism selectively deploys one or more of the at least two needles between the retracted and the extended position. Still further, the needle deployment mechanism may
10 include at least one of a pneumatic piston, an electric motor, and a spring.

The device may include at least one pressure sensor for measuring tissue apposition pressure. The sensor may be provided on either or both of the housing and the needle array. Deployment of the at least one needle may be inhibited if a measured apposition pressure values falls beneath an initial threshold value or exceeds a secondary threshold
15 value. The device may include two or more sensors wherein deployment of the at least one needle is inhibited if a difference in measured apposition pressure values between any two sensors exceeds a threshold value.

The aforementioned mixing means may include at least one of a blade, paddle, whisk, and semi-permeable membrane positioned within the mixing chamber. The mixing
20 means may further include one of a motor and a pneumatic source operably coupled to the at least one of a blade, paddle, whisk, and semi-permeable membrane.

The device of the present invention may include tissue apposition means for pulling the needle array into apposition with tissue. The tissue apposition means may include at least one vacuum orifice defined in at least one of the housing and the needle
25 array, whereby the vacuum orifice transmits suction from a source of partial vacuum to tissue bringing the needle array into apposition with the tissue. The vacuum orifice may be formed in the needle array, and the at least one needle may be positioned within the vacuum orifice. Still further, the vacuum orifice may define a receptacle, whereby tissue is pulled at least partially into the receptacle when the vacuum orifice transmits suction from
30 the source of partial vacuum.

In some embodiments, the needle array includes a tissue apposition surface; and the tissue apposition means further includes at least one flange mounted on the tissue apposition surface and surrounding the vacuum orifice.

The device of the present invention may include means for adjusting a needle insertion depth of the at least one needle. The needle array may include at least two needles and the insertion depth adjustment means may individually adjust the insertion depth of each needle. In one embodiment, the needle insertion depth adjustment means may include a plurality of discrete needle adjustment depths. Alternatively, the needle insertion depth adjustment means provides continuous adjustment of the needle adjustment depth. Still further, the needle insertion depth adjustment means may include a readout and/or a display indicative of the needle adjustment depth.

According to one embodiment, the needle array includes a tissue apposition surface; and the at least one needle includes a distal end, the at least one needle being moveable between a retracted position in which the distal end of the needle is maintained beneath the tissue apposition surface and an extended position in which the distal end of the needle extends beyond the tissue apposition surface.

According to one embodiment an ultrasound transducer is operably connected to one of the needle array, the housing and the at least one needle.

According to one aspect, the needle array may generally surround the ultrasound transducer. Alternatively, the ultrasound transducer may generally surround the needle array. Moreover, the ultrasound transducer may be integrally formed with the needle array.

The device may further include a fluid pressurization mechanism in fluid communication with the at least one needle.

Still further, the device may include means for controlling a volume and pressure of fluid dispensed from the fluid reservoir into the mixing chamber. Moreover the device may include means for controlling the volume, pressure, and rate at which fluid or solution is injected into the tissue.

A machine readable identifier may be provided on the needle array. The identifier may be used to uniquely identify the ultrasound transducer, needle array and/or characteristics of the needle array.

According to one embodiment, the device includes a machine readable identifier on the needle array and means for reading the identifier operably connected to the needle deployment mechanism. Optionally, the needle deployment mechanism inhibits deployment of the at least one needle unless the identifier reading means authenticates the identifier. Moreover, the needle deployment mechanism may optionally accumulate the number of times the needle array associated with a given identifier is deployed and inhibit

deployment of the at least one needle if the accumulated number needle deployments associated with the identifier exceeds a predetermined value.

According to one embodiment, the device includes a machine readable identifier on the needle array and means for reading the identifier operably connected to the fluid
5 pressurization mechanism, wherein the fluid pressurization mechanism adjusts the fluid injection pressure in response to information read from the identifier.

Also disclosed is a system comprising, a container containing a measured amount of a solution including at least one of a vasoconstrictor, a surfactant, and an anesthetic, the solution comprising a liquid and at least one of a gas and a fluid; a needle array in fluid
10 connection with the container, the needle array including at least one needle. The gas is at least partially dissolved and may be fully dissolved in the fluid. Optionally, the solution container is enclosed, and the solution is maintained at greater than atmospheric pressure.

The aforementioned system may include an ultrasound transducer apparatus capable of operating in at least one of first, second, third, and fourth energy settings,
15 wherein the first energy setting is selected to facilitate the absorption of solution by the tissue, the second energy setting is selected to facilitate stable cavitation, the third energy setting is selected to facilitate transient cavitation, and the fourth energy setting is selected to facilitate pushing bubbles within tissue. The transducer apparatus may include first and second transducers, wherein the first transducer facilitates popping of bubbles and the
20 second transducer facilitates bringing dissolved gas out of solution. According to one embodiment, the transducer apparatus produces at least one of unfocussed and defocused ultrasound waves.

Also disclosed is a method for selectively lysing cells, comprising: percutaneously injecting a solution including at least one of a vasoconstrictor, a surfactant, and an
25 anesthetic into subcutaneous tissue, insonating the tissue with ultrasound setting to distribute the solution by acoustic radiation force; and insonating the tissue at a second ultrasound setting to induce cell uptake of the solution and thereby lyse the cells.

Also disclosed is a method for selectively lysing cells, comprising: percutaneously injecting a microbubble solution into subcutaneous tissue; insonating the tissue at a first
30 ultrasound setting to distribute the solution and push the microbubble against walls of the cells by acoustic radiation force; and insonating the tissue at a second ultrasound setting to induce transient cavitation. The solution may include at least one of a vasoconstrictor, a surfactant, and an anesthetic.

Also disclosed is a method for selectively lysing cells, comprising: percutaneously injecting a solution into subcutaneous tissue, the solution containing at least one of a dissolved gas and a partially dissolved gas; insonating the tissue to induce stable cavitation and generate microbubbles; insonating the tissue with ultrasound to distribute the solution and push the microbubble against walls of the cells by acoustic radiation force; insonating the tissue with ultrasound to induce transient cavitation. The solution may include at least one of a vasoconstrictor, a surfactant, and an anesthetic.

Each of the aforementioned embodiments may include a needle or needles having a texture encouraging the creation of microbubbles.

BRIEF DESCRIPTION OF THE DRAWINGS

Further features of the invention, its nature and various advantages will be more apparent from the accompanying drawings and the following detailed description, in which:

FIGs. 1A and 1B are block diagrams of a bubble generator according to the present invention;

FIG. 1C is a block diagram of a first modification of the bubble generator of FIG. 1B;

FIG. 1D is a block diagram of a second modification of the bubble generator of FIG. 1B;

FIG. 2 is a block diagram of a tissue cavitation system according to the present invention;

FIGs. 3A-3C are views of a fluid injection device including a manifold and an injection depth adjustment mechanism according to the present invention;

FIGs. 3D shows a modified mechanism for adjusting the injection depth of the fluid injection device of FIG. 3A;

FIGs. 4A-4C show an alternate embodiment fluid injection device including a mechanism for individually adjusting the fluid flow through each needle and a mechanism for individually adjusting the injection depth;

FIG. 5 shows a needle array including an optional sensor used in a fluid injection device according to the present invention;

FIGs. 6A and 6B show straight and side firing needles used in the needle array of FIG. 5;

FIG. 7 is a block diagram a fluid injection device including a mechanism for rotating the needle in situ;

FIGs. 8A and 8B show the fluid injection device in a retracted and fully extended position;

FIGs. 9A-9C show a tissue apposition mechanism according to the present invention;

5 FIGs. 10A and 10B show an alternate embodiment bubble generator and a system for injecting and insonating bubbles using the same;

FIG. 11 shows a counterbalance arm for supporting a solution injection and insonation system according to the present invention;

10 FIGs. 12A and 12B show a handpiece including a fluid injection mechanism used as part of a solution injection and insonation system of the present invention;

FIG. 13 is a block diagram of an alternate embodiment of the tissue cavitation system which does not utilize a bubble generator; and

FIG. 14 is a section view of a transducer apparatus according to the present invention.

15 DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

One aspect of the present invention relates to a device for generating a microbubble solution and for a system using the device to selectively lyse tissue.

20 According to a first embodiment of the invention the microbubble solution includes a fluid or mixture containing one or more of the following: active bubbles, partially dissolved bubbles, a saturated or supersaturated liquid containing fully dissolved bubbles or a material/chemical which generates bubbles in situ. The bubbles may be encapsulated within a lipid or the like, or may be unencapsulated (free) bubbles.

25 Active bubbles refer to gaseous or vapor bubbles which may include encapsulated gas or unencapsulated gas. These active bubbles may or may not be visible to the naked eye. Dissolved bubbles refer to gas which has dissolved into the liquid at a given pressure and temperature but which will come out of solution when the temperature and/or pressure of the solution changes or in response to ultrasound insonation. The microbubbles may come out of solution in situ, i.e., after the solution is injected into the tissue. This may, for example, occur when the solution reaches the temperature of the tissue or when the tissue
30 is subjected to ultrasound insonation. Alternatively, the microbubble may come out of solution before the solution is injected into the tissue when reaching atmospheric pressure. Thus, the bubbles may come out of solution before or after the solution is injected into the tissue.

As noted, the solution includes a liquid (fluid) and a gas which may or may not be dissolved in the liquid. By manner of illustration, the liquid portion of enhancing agent may include an aqueous solution, isotonic saline, normal saline, hypotonic saline, hypotonic solution, or a hypertonic solution. The solution may optionally include one or
5 more additives/agents to raise the pH (e.g., sodium bicarbonate) or a buffering agent such as known in the art. By manner of illustration the gaseous portion of the solution may include air drawn from the room ("room air" or "ambient air"), oxygen, carbon dioxide, perfluoropropane, argon, hydrogen, or a mixture of one or more of these gases. However, the invention is not limited to any particular gas. There are a number of candidate gas and
10 liquid combinations, the primary limitation being that both the gas and the liquid must be biocompatible, and the gas must be compatible with the liquid.

According to a presently preferred embodiment the liquid portion of the microbubble solution includes hypotonic buffered saline and the gaseous portion includes air.

15 It should be noted that the biocompatibility of overall solution depends on a variety of factors including the biocompatibility of the liquid and gas, the ratio of gas to liquid, and the size of the microbubbles. If the microbubbles are too large they may not reach the target tissue. Moreover, if the bubbles are too small they may go into solution before they can be used therapeutically. As will be explained in further detail below, the microbubble
20 solution of the present invention may include a distribution of different sized microbubbles. Thus it is anticipated that the solution may contain at least some microbubbles which are too small to be therapeutically useful as well as some which are larger than the ideal size. It is anticipated that a filter, filtering mechanism or the like may be provided to ensure that bubbles larger than a threshold size are not injected into the
25 tissue.

It should further be appreciated that "biocompatible" is a relative term in that living tissue may tolerate a small amount of a substance whereas a large amount of the same substance may be toxic with both dose and dosage as considerations. Thus, the biocompatibility of the microbubble solution of the present invention should be interpreted
30 in relation to the amount of solution being infused, the size of the microbubbles, and the ratio of gas to liquid. Moreover, since selective cell lysis is one of the objects of the present invention, the term biocompatible should be understood to include a mixture or solution which may result in localized cell lysis alone or in conjunction with ultrasound insonation.

The microbubble solution according to the present invention may include one or more additives such as a surfactant to stabilize the microbubbles, a local anesthetic, a vasodilator, and a vasoconstrictor. By manner of illustration the local anesthetic may be lidocaine and the vasoconstrictor may be epinephrine. Table 1 is a non-exclusive list of other vasoconstrictors which may be included in the microbubble solution of the present invention. Table 2 is a non-exclusive list of other local anesthetics which may be included in the microbubble solution of the present invention. Table 3 is a non-exclusive list of gaseous anesthetics which may be included in the gaseous portion of the solution of the present invention. Table 4 is a non-exclusive list of surfactants which may be included in the solution of the present invention.

Table 1

<u>Vasoconstrictors</u>
Norepinephrine
Epinephrine
Angiotensin II
Vasopressin
Endothelin

Table 2

<u>Anesthetics (Local)</u>
Amino esters
Benzocaine
Chlorprocaine
Cocaine
Procaine
Tetracaine
Amino amides
Bupivacaine
Levobupivacaine
Lidocaine
Mepivacaine
Prilocaine
Ropivacaine
Articaine
Trimecaine

5

Table 3

<u>Anesthetics (gaseous)</u>
Halothane
Desflurane
Sevoflurane
Isoflurane
Enflurane

10

Table 4

Surfactants

Anionic (based on sulfate, sulfonate or carboxylate anions)

Sodium dodecyl sulfate (SDS), ammonium lauryl sulfate, and other alkyl sulfate salts

Sodium laureth sulfate, also known as sodium lauryl ether sulfate (SLES)

Alkyl benzene sulfonate

Soaps, or fatty acid salts

Cationic (based on quaternary ammonium cations)

Cetyl trimethylammonium bromide (CTAB) a.k.a. hexadecyl trimethyl ammonium bromide, and other alkyltrimethylammonium salts

Cetylpyridinium chloride (CPC)

Polyethoxylated tallow amine (POEA)

Benzalkonium chloride (BAC)

Benzethonium chloride (BZT)

Zwitterionic (amphoteric)

Dodecyl betaine

Dodecyl dimethylamine oxide

Cocamidopropyl betaine

Coco ampho glycinate

Nonionic

Alkyl poly(ethylene oxide) called Poloxamers or Poloxamines)

Alkyl polyglucosides, including:

Octyl glucoside

Decyl maltoside

Fatty alcohols

Cetyl alcohol

Oleyl alcohol

Cocamide MEA, cocamide DEA, cocamide TEA

The enhancing solution may further include a buffering agent such as sodium bicarbonate. Table 5 is a non-exclusive list of buffers which may be included in the solution of the present invention.

Table 5

Buffer	
H ₃ PO ₄ / NaH ₂ PO ₄ (pK _{a1})	NaH ₂ PO ₄ / Na ₂ HPO ₄ (pK _{a2})
1,3-Diaza-2,4-cyclopentadiene and Glyoxaline (Imidazole)	N-Tris(hydroxymethyl)methyl-2-aminoethanesulfonic acid (TES)

ampholyte N-(2-hydroxyethyl) piperazine-N'-2-hydroxypropanesulfonic acid (HEPPSO)	N-2-Hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES)
Acetic acid	Citric acid (pK _{a1})
N-Tris(hydroxymethyl)methyl-3-aminopropanesulfonic acid (TAPS)	Triethanolamine (2,2',2''-Nitrilotriethanol Tris(2-hydroxyethyl)amine)
Bis(2-hydroxyethyl)iminotris(hydroxymethyl)methane (Bis-Tris)	N-[Tris(hydroxymethyl)methyl]glycine, 3-[(3-Cholamidopropyl)dimethylammonio]propanesulfonic acid (Tricine)
Cacodylic acid	2-Amino-2-(hydroxymethyl)-1,3-propanediol (Tris)
H ₂ CO ₃ / NaHCO ₃ (pK _{a1})	Glycine amide
Citric acid (pK _{a3})	N,N-Bis(2-hydroxyethyl)glycine (Bicine)
2-(N-Morpholino)ethanesulfonic Acid (MES)	Glycylglycine (pK _{a2})
N-(2-Acetamido)iminodiacetic Acid (ADA)	Citric acid (pK _{a2})
Bis-Tris Propane (pK _{a1})	Bis-Tris Propane (pK _{a2})
Piperazine-1,4-bis(2-ethanesulfonic acid) (PIPES)	N-(2-Acetamido)-2-aminoethanesulfonic acid (ACES)
Boric acid (H ₃ BO ₃ / Na ₂ B ₄ O ₇)	N-Cyclohexyl-2-aminoethanesulfonic acid (CHES)
Glycine (pK _{a1})	Glycine (pK _{a2})
N,N-Bis(2-hydroxyethyl)-2-aminoethanesulfonic acid (BES)	NaHCO ₃ / Na ₂ CO ₃ (pK _{a2})
3-Morpholinopropanesulfonic acid (MOPS)	N-Cyclohexyl-3-aminopropanesulfonic acid (CAPS)
Na ₂ HPO ₄ / Na ₃ PO ₄ (pK _{a3})	Hexahydropyridine (Piperidine)

*The anhydrous molecular weight is reported in the table. Actual molecular weight will depend on the degree of hydration.

It should be noted that like reference numerals are intended to identify like parts of the invention, and that dashed lines are intended to represent optional components.

5 FIG. 1A depicts a first embodiment of a device 100 for generating microbubbles in the enhancing solution. The device 100 consists of a liquid reservoir 102, a gas vapor

reservoir 104 (shown in dashed lines) and a bubble generator 106. The bubble generator 106 is a vessel or vessels in which the fluid and gas are mixed. Fluid from the liquid reservoir 102 and gas/vapor from the gas reservoir 104 flow into the bubble generator 106 and are mixed to create microbubbles and/or supersaturate the fluid.

5 The device 100 may include a fluid metering device 124 (shown in dashed lines) controlling the amount of fluid dispensed into the bubble generator 106 and/or a fluid metering device 126 (shown in dashed lines) controlling the amount of microbubble solution to be injected into the tissue. The device 100 may further include a gas metering device 128 (shown in dashed lines) used to control the amount of gas dispensed into the
10 bubble generator 106. The device 100 depicted in FIG. 1A includes both of the fluid metering devices 124 and 126 and the gas metering device 128; however, in practice one or more of these devices may be eliminated. As noted previously, two or more components may be integrated together. For example, the fluid metering device 124 may be integrated into the fluid injection device 202.

15 FIG. 1B is a more detailed illustration of a first embodiment of the bubble generator 106 and includes a housing 108, a pair of cylinders 116 interconnected by a pathway 118. At least one of the cylinders 116 is in fluid communication with the liquid reservoir 102, and at least one of the cylinders 116 is in fluid communication with the gas reservoir 104 (which may be ambient environment). The fluid pathway 118 provides fluid
20 communication between the cylinders 116.

One or more of the cylinder(s) 116 may be provided with a reciprocating piston 120 driven by an external power source 122 such as a source of compressed air, spring, elastomeric member, motor, stepper motor or the like. According to one embodiment, the reciprocating piston 120 is a pneumatic piston manufactured by the Bimba Corporation.

25 Liquid from the liquid reservoir 102 may be pushed into the bubble generator 106 under positive pressure from an external pressurization source 110 (shown in dashed lines); it can be drawn into the bubble generator 106 under partial pressure which may for example be generated by the reciprocating piston 120; or it can flow into the generator 106 under gravity. Similarly, gas from the gas reservoir 104 may be pushed into the bubble
30 generator 106 under positive pressure from an external pressurization source 112 (shown in dashed lines) or it can be drawn into the bubble generator 106 under partial pressure. As will be described below, the piston 120 may also serve a dual purpose as a fluid pressurization mechanism for injecting the fluid into the tissue.

The bubble generator 106 may or may not be pressurized to enhance the saturation of the gas in the solution or prevent dissolved gas from coming out of solution. An optional fluid pressurization mechanism 110 (shown in dashed lines) may be used to maintain the fluid at a desired pressurization. As will be described in further detail below,
5 the fluid may be chilled to further enhance solubility/saturation of the gas in the solution.

FIG. 1C is an alternate embodiment of the microbubble generator 106, which utilizes a member 120' (rotor) such as a blade, paddle, whisk, semi-permeable membrane or the like driven by an external power source 122 to generate the microbubbles within a cylinder or mixing chamber (stator) 116. As will be appreciated by one of ordinary skill in
10 the art the member 120' is rotationally driven by the external power source 122 within a cylinder 116 or the like. An optional fluid pressurization mechanism 130 may be used for injecting the fluid into the tissue.

The fluid in the reservoir 102 may be at ambient temperature. Alternatively, the fluid may be chilled slightly to enhance gas solubility (super saturation). The fluid
15 reservoir 102 may be thermally insulated to maintain the fluid at its present temperature and or/ the fluid reservoir 102 may include a heating/cooling mechanism (not illustrated) to maintain the fluid at a predetermined temperature.

If the gas used is air then the gas reservoir 104 may be eliminated in favor of simply drawing air from the environment, i.e., the room housing the device 100 ("room
20 air"). If room air is used, the device 100 may include an air filter 114 (shown in dashed lines) such as a HEPA filter or the like.

FIG. 1D is an alternate embodiment of the microbubble generator 106, which utilizes an agitator 133 to agitate or shake a container or cartridge 132 containing measured amounts of liquid and gas and generate the microbubbles within the cartridge
25 132. The microbubble solution is dispensed from the cartridge 132 to fluid injection device 202 (FIG. 2). Additionally, this cartridge 132 may incorporate an active heating/cooling mechanism to control the temperature of the fluid at a predetermined setting. Furthermore, the cartridge 132 may be pressurized, such as by compressed air or mechanical mechanism to allow dispensation of the contents at a predetermined rate and
30 pressure.

FIG. 2 is a block diagram of a liposculpture system 200 according to the present invention. The system 200 includes device 100, a fluid injection device 202, an ultrasound transducer apparatus 204, an ultrasound generator 206, an ultrasound control unit 208, and

an injection control unit 210. Device 100 may include the bubble generator 106 depicted in FIGs. 1A – 1D or may be one of the alternative embodiments disclosed herein below.

5 The fluid injection device 202 may include a needle array 214 which may include one or more needles 218. Alternatively, the fluid injection device 202 may, for example, include one or more hypodermic syringes.

The fluid injection device 202 further includes or is operably connected to a fluid pressurization mechanism 110 for pushing the solution into the tissue. As noted above, the piston 120 or the like used to express fluid between the cylinders 116 may serve as the fluid pressurization mechanism 210.

10 One or more of the components collectively termed system 200 may be combined. For example the fluid injection device 202 may be integrated as a single component with the ultrasound transducer apparatus 204 and/or the fluid injection control unit 210. Likewise, the ultrasound control unit 208 can be integrated as a single component with the ultrasound generator 206. Such integration of components is contemplated and falls within
15 the scope of the present invention.

The fluid injection control unit 210 may control the amount of fluid and gas dispensed into the bubble generator 106 and/or the amount of solution injected into the tissue. Optionally, the control unit 210 may be interfaced directly or indirectly with the fluid metering device(s) 124, 126 and the gas metering device 128. The fluid injection
20 control unit 210 may control the mixing or agitation (if any) of the solution within the bubble generator 106. The fluid injection control unit 210 may control the injection of solution into the tissue 220 by the injection device 202, including the deployment of a needle array 214, the depth to which the needle array 214 is deployed, and the amount of solution injected.

25 The fluid injection control unit 210 may control the individual deployment and retraction of one more needles (or hypodermic syringes) of the needle array 214. Thus, the control unit 210 may deploy or retract the needles 218 (or hypodermic syringes) one at a time, may deploy or retract two or more needles 218 at a time, or may deploy or retract all of the needles simultaneously.

30 Additionally, the fluid injection control unit 210 may individually control the amount of solution delivered to each needle 218. One of ordinary skill in the art will appreciate that there are many ways to control the amount of solution delivered to each needle 218. For example, it may be desirable to deliver more solution in the center of the treatment area and less to the peripheral portion of the treatment area or vice-versa.

If the injection device 202 utilizes hypodermic syringes, then the fluid injection control unit 210 may control the amount of fluid distributed to each syringe. As noted above it may be desirable to provide differing amounts of solution to different areas of the treatment area, and this may be achieved by varying the amount of solution in each syringe.

As best seen in FIGs. 3A-3C, the fluid injection device 202 may include a manifold or fluid distribution pathway 212 (shown in dashed lines) in fluid connection with device 100 and needle array 214, and a needle deployment mechanism 216 operably connected to the needle array 214. The manifold 212 is the fluid pathway used to transport the microbubble solution from the microbubble generator 106 to the needle array 214.

One or more flow control devices 222 may be provided in the fluid pathway 212 to enable individualized control of the amount of fluid dispensed to each of the needles or syringes 218. The manifold 212 alone or in combination with the flow control devices 222 controls the distribution of the microbubble solution among the needles 218. The manifold 212 may be configured to deliver a uniform amount of solution to each of the needles 218 (or hypodermic syringes), or it may be configured to deliver differing amounts of solution to different needles 218. The flow control devices 222 may be manually adjustable and/or may be controlled by the injection control unit 210. An alternate embodiment may include infinitely variable volume control at each needle or hypodermic through active means, such as with an electronic flow meter and controller.

It may be desirable to deploy all of the needles 218 simultaneously into the tissue but deliver solution to one or more needles 218 individually. For example, it may be desirable to deliver solution sequentially to groups of one or more needles 218. If needles 218 are deployed individually or in groups of two or more it may be desirable to deliver solution only to the deployed needles 218.

As will be explained below, the injection depth may be manually determined by selecting an appropriate needle length or setting a desired injection depth.

The needle deployment mechanism 216 (FIGs. 2 and 3A) deploys one or more needles 218 (or hypodermic syringes) of the needle array 214 such that needles 218 penetrate a desired distance into the tissue. The needle deployment mechanism 216 may be configured to deploy the needle(s) 218 to a fixed predetermined depth or may include means for adjusting the depth that the needle(s) 218 are deployed.

There are several broad approaches for adjusting the injection depth which may be utilized. One way to adjust the injection depth is to provide needle arrays 214 of varying

length needles. According to this embodiment, the user simply selects an array 214 having shorter/longer needles 218 to achieve a desired injection depth. Moreover, the different length needles 218 may be used within a given array 214.

5 According to another approach, the needle array 214 is displaced vertically in order to adjust the injection depth.

FIG. 3A shows aspects of an adjusting means, which may include a flange 244A and a groove 244B arrangement for vertically adjusting the needle array in discrete intervals.

10 FIG. 3D shows aspects of an adjusting means, which may include mating screw threads 240 formed on the needle array 214 and the fluid injection device 202 or housing 108 which enable the user to vertically adjust the needle array 214 thereby altering the injection depth.

According to one embodiment, the injection depth may be continuously adjusted within a given range of injection depths. For example, the user may be able to continually
15 adjust the injection depth between 5 and 12 millimeters by rotating the needle array 214. According to an alternate embodiment, the injection depth may be adjusted in discrete intervals. For example, the user may be able to adjust the injection depth between 3 and 15 millimeters in 1 millimeter increments. In yet another embodiment, the needle depth may be controlled electronically whereby the user enters a specified depth on the control
20 unit 210.

The injection depth adjustment described above may specify the injection depth for the entire needle array 214. However, according to yet another approach it may be desirable to facilitate the individualized adjustment of one or more needles 218 of the needle array 214. The needle deployment mechanism 216 may allow for the independent
25 adjustment of the injection depth for one or more of the needles 218 or syringes.

One or more of the needles 218 or syringes may be displaced vertically in order to adjust the injection depth of individual needles. The adjustment of the injection depth (vertical needle displacement) may be continuous or in discrete intervals, and may be manual or may be adjusted via the injection control unit 210.

30 As noted above, the injection depth may be adjusted by providing mating screw threads 246 to dial in the desired injection depth (FIG. 4A), a standoff 248 to provide a means for adjusting the injection depth in discrete intervals (FIG. 4B), or the like on the needle array 214 to adjust the vertical height of the needles 218 relative to the tissue apposition surface 226A.

Yet another approach to individualized injection depth control is to deploy individual needles or syringes 218 as opposed to deploying the entire needle array 214. The injection control unit 210 or needle deployment mechanism 216 selects the injection depth of each individual needle or syringe 218 (FIG. 4C).

5 One of ordinary skill in the art will appreciate that there are many other ways to implement the adjustment of the injection depth. The invention is not limited to the embodiments depicted in the drawings.

The needle deployment mechanism 216 deploys the needles 218 in response to a signal from the fluid injection control unit 210. The deployment mechanism 216 may
10 include a spring, pneumatic ram, or the like which deploys the needles 218 with sufficient force to penetrate the tissue 220. The fluid injection control unit 210 synchronizes the deployment mechanism 216 with the injection of the microbubble solution into the tissue.

A predetermined amount of the solution may be injected at a single injection depth. Alternatively, the fluid injection control unit 210 in synchronism with the deployment
15 mechanism 216 may inject solution at each of plural injection depths, or may inject continuously as the needle array 214 on either the forward (penetration) or rearward (withdrawal) strokes. It may be desirable to deploy the needles to a first depth within the tissue and then retract the needles to a slightly shallower injection depth before injecting the solution.

20 FIG. 5 is an enlarged view of the needle array 214 including at least one hypodermic needle or micro-needle 218. The invention is not limited to any particular length or gauge needle, and needles 218 are selected in accordance with the depth of the tissue to be treated and to accommodate patient comfort. Moreover, it may be desirable for the needle array 214 to include needles of varying length and/or needles of varying
25 gauge.

The embodiment depicted in FIG. 5 includes a plurality of uniformly spaced needles 218. However, the scope of the invention is not limited to any particular number of needles 218; moreover, the invention is not limited to any particular geometric arrangement or configuration of needles 218. It may be desirable to have non-uniform
30 needle spacing. For example, it may be desirable to have a smaller (denser) needle spacing in one portion of the treatment region and a greater (sparser) needle spacing in another portion. The use of additional needles 218 may facilitate uniform distribution of the microbubble solution in the tissue 220 and/or reduce the number of distinct injection cycles needed to treat a given area.

FIG. 6A depicts a needle 218 having a single injection orifice 242, which is linearly aligned with the needle shaft 224. The hypodermic needle 218 is a tubular member having a lumen configured for injection of the solution through the needle and into the tissue. The lumen may include a textured surface for promoting the generation of microbubbles.

FIG. 6B depicts an alternative needle 218A having one or more side firing orifice(s) 242A which are generally orthogonal to longitudinal axis of the shaft 224A. The side firing orifice(s) may be formed at different heights along the length of the needle shaft such that solution is injected at varying injection depths. These orifice(s) may also be arranged in a specific radial pattern to preferentially direct the flow distribution.

Depending on the characteristics of the tissue undergoing treatment the user may find that needle 218 is preferable over needle 218A or vice versa. Reference to the needles 218 should be understood to refer generally to both the needles 218 (FIG. 6A) and the needles 218A (FIG. 6B).

As shown in FIG. 7, some embodiments of the invention may include a mechanism 256 for selectively rotating one or more of the needles 218 in situ. This feature may facilitate the uniform distribution of solution in the tissue.

According to some embodiments of the invention it may be desirable for the needle deployment mechanism 216 to ultrasonically vibrate one or more of the needles 218. This feature may facilitate tissue penetration and/or bringing dissolved gas out of solution. For example, an ultrasound transducer 258 may be operably coupled to the needles 218 and/or the needle array 214. The ultrasound transducer 258 is shown for the sake of convenience in FIG. 7 however, the transducer 258 may be used in a device which does not include the needle rotation mechanism 256 and vice versa.

As best seen in FIG. 8A, the hypodermic needle 218 has a proximal end connected to the fluid distribution pathway 212 and a distal end configured for penetrating into the tissue 220 to be treated. In one embodiment, the needles 218 may include micro-needles.

In one embodiment, the fluid injection device 202 includes needle deployment mechanism 216 for moving the hypodermic needle 218 from a fully retracted position (FIG. 8A) in which the distal end of the needle 218 is housed inside the solution injection member 202 to a fully extended position (FIG. 8B).

As shown in FIGs. 9A-9C, the fluid injection device 202 may optionally be provided with a tissue apposition mechanism which urges the device 202 into firm apposition with the tissue 220 undergoing treatment. According to one embodiment the

tissue apposition mechanism includes at least one vacuum port 228 and a vacuum source 230 in fluid communication with the vacuum port 228. The vacuum port 228 may be defined in the needle array 214 and/or the housing 108. In operation the tissue apposition surface 226A is pulled into apposition with the tissue 220 when vacuum from the vacuum source 230 is transmitted through the vacuum port 228 to the tissue 220.

In some embodiments it may be desirable to provide a one-to-one relationship between needles 218 and vacuum ports 228. Moreover, the needle(s) 218 may be positioned within the vacuum port(s) 228. The vacuum port 228 may define a recess or receptacle 229 such that the tissue 220 is at least partially pulled (sucked) into the recess 229 by the vacuum force. Moreover, the needles 218 may be at least partially housed within and deployed through the recess 229.

An optional flange 232 (show in dashed lines) may surround (skirt) the periphery of the needles 218 (or 218A) to channel/contain the suction force. Alternatively, a separate flange 232A may surround (skirt) each of the needles 218 (or 218A) to channel/contain the suction force.

It may be desirable to have one or more vacuum ports 228 spaced along a periphery of the apposition surface 226A. Moreover, it may be desirable to include a central portion apposition surface 226A, which does not include any vacuum ports 228 (no suction zone). Alternatively, it may be desirable to have vacuum ports confined to a central portion of the apposition surface 226A.

It should be appreciated that the liquid reservoir 102 and gas reservoir 104, in each of the aforementioned embodiments may be replaced with a cartridge 132 (FIG. 1D) containing a pre-measured amount of liquid and gas. The gas may be fully or partially dissolved in the fluid. In its simplest form the cartridge 132 is simply a sealed container filled with a predetermined amount of gas and liquid, e.g., a soda can.

FIG. 10A shows an enhanced cartridge 106A (“Guinness can”), which may be used to replace the liquid reservoir 102, gas reservoir 104, and bubble generator 106 in each of the aforementioned embodiments. In this embodiment, the cartridge 106A includes a hollow pressurized pod 134 such as disclosed in U.S. 4,832,968, which is hereby incorporated by reference. Both the cartridge 106A and the pod 134 contain a solution of gas and liquid under greater than ambient pressure which may for example be achieved by providing or introducing a dose of liquid nitrogen into the solution before sealing the cartridge 106A.

The cartridge 106A includes a headspace 136, which is bounded between a top inner surface 138 and a gas-liquid interface 140. The pod 134 includes a similar headspace 142, which is bounded between a top inner surface 144 and a gas-liquid interface 146.

5 The pod 134 includes a small opening or orifice 148, which enables the pressure within the headspace 136 of the cartridge 106A to reach equilibrium with the pressure within the headspace 142 of the pod 134. When a seal 150 of the cartridge 106A is pierced the pressure within the headspace 136 rapidly reaches equilibrium with the ambient pressure. In the moments after seal 150 is pierced the pressure within the pod 134 is
10 greater than the pressure in the headspace 136 of the cartridge 106A because the orifice 148 restricts the rate of flow of solution out of the pod 134. A jet of solution forcefully streams out of the orifice 148 into the solution within the cartridge 106A, which agitates and/or shears the solution within the cartridge causing some of the dissolved bubbles to come out of solution thereby generating microbubbles in the solution.

15 The pod 134 is preferably situated at or near the bottom of the cartridge 106A such that the orifice 148 is maintained below the liquid gas interface 140.

FIG. 10B is a block diagram showing the system 200 including cartridge 106A in place of bubble generator 106.

The microbubble generator 106 may be mounted on (integrated with) the fluid
20 injection device 202 thereby minimizing the distance that the solution travels before being injected into the tissue. The liquid reservoir 102 and gas reservoir 104 (if provided) may be removably connected to the microbubble generator 106 as needed to generate microbubble solution. The injection device 202 may be manually supported by the operator. Alternatively, the injection device 202 may be supported on an arm 302 (FIG.
25 11) which may include a counterbalance to facilitate manipulation of the injection device 202.

FIG. 12A depicts a handpiece 300 which includes fluid injection device 202 and which is coupled to the microbubble generator 106 (not illustrated) by a flexible conduit 236. This design minimizes the size and weight of handpiece 300 being handled by the
30 operator since the handpiece 300 does not include the microbubble generator 106.

FIG. 12B depicts a handpiece 300 using the cartridge 106A mounted on the fluid injection device 202. This embodiment minimizes the distance that the microbubble solution travels before being injected into the tissue.

According to one embodiment the system of the invention includes a container which may be an enclosed or sealed cartridge 106A or it may be an open container. If the container is sealed it includes a measured amount of a solution. Obviously, if the container is not sealed then solution may be freely added as needed.

5 The system includes a needle array including at least one needle. The needle array 214 being in fluid connection with the container.

The solution includes any of the solutions disclosed herein. The solution includes a liquid. The solution may further include a gas which may be partially or fully dissolved within the solution.

10 The container may be enclosed and the solution may be maintained at greater than atmospheric pressure.

The needle array 214 includes at least one needle 218 which may be any of the needles disclosed herein.

15 The aforementioned gas may include one or more gases selected from the group of air, oxygen, carbon dioxide, carbon dioxide, perfluoropropane, argon, hydrogen, Halothane, Desflurane, Sevoflurane, Isoflurane, and Enflurane.

The solution may include one or more of a vasoconstrictor, a surfactant, and an anesthetic. Moreover, the vasoconstrictor may include one or more of Norepinephrine, Epinephrine, Angiotensin II, Vasopressin and Endothelin.

20 Optionally, the system may include refrigeration means for maintaining the container at a predefined temperature range. Moreover, the container may be thermally insulated.

The system may further include an ultrasound transducer apparatus 204 for transmitting ultrasound waves to the tissue. Preferably, the transducer apparatus 204 is
25 operated in synchronism with the injection of solution into the tissue.

The transducer apparatus 204 may transmit ultrasound energy at a first setting to facilitate the distribution, absorption and/or uptake of solution by the tissue, i.e., sonoporation.

30 Ultrasound parameters that enhance the distribution of the solution include those conditions which create microstreaming, such as large duty cycle pulsed ultrasound (> 10% duty cycle) or continuous wave ultrasound at a range of frequencies from 500 kHz to 15 MHz, focused or unfocused, and a mechanical index less than 4. According to one embodiment the mechanical index (MI) falls within the range $.5 \leq MI \leq 4$. According to another embodiment the mechanical index falls within the range $.5 \leq MI \leq 1.9$.

Sonoporation leading to increased absorption and/or uptake of the solution in the tissue can be generated by pulsed wave or continuous wave ultrasound, at a range of frequencies from 500 kHz to 15 MHz, focused or unfocused and medium to high mechanical index ($MI > 1.0$). The preferred embodiment is pulsed wave ultrasound at a frequency of 500 kHz, unfocused, with high mechanical index ($MI > 1.9$) in order to reproducibly create pores that are temporary or longer lasting pores.

The transducer apparatus 204 may transmit ultrasound energy at a second setting to facilitate the generation of bubbles by bringing dissolved gas out of solution, i.e., stable cavitation.

Ultrasound parameters for stable cavitation such as large duty cycle pulsed ultrasound ($> 10\%$ duty cycle) or continuous wave ultrasound at a range of frequencies from 2MHz to 15 MHz, focused or unfocused, and a mechanical index (MI) $.05 \leq MI \leq 2.0$.

The transducer apparatus 204 may transmit ultrasound energy at a third setting to facilitate transient cavitation, i.e., popping bubbles.

Ultrasound parameters for transient cavitation at a range of frequencies from 500kHz to 2 MHz, focused or unfocused, and a mechanical index (MI) greater than 1.9. The duty cycle required for transient cavitation may be very low, and the preferred embodiment is a wideband pulse (1 to 20 cycles) transmitted at a duty cycle less than 5%.

The transducer apparatus 204 may include any of the transducers disclosed herein, and may be operably connected to the needle array 214.

The transducer apparatus 204 may transmit ultrasound energy at a fourth frequency range to facilitate the pushing of bubbles within the tissue by acoustic streaming and/or acoustic radiation force.

Ultrasound Acoustic Streaming and Radiation Force

Sound propagating through a medium produces a force on particles suspended in the medium, and also upon the medium itself. Ultrasound produces a radiation force that is exerted upon objects in a medium with an acoustic impedance different than that of the medium. An example is a nanoparticle in blood, although, as one of ordinary skill will recognize, ultrasound radiation forces also may be generated on non-liquid core carrier particles. When the medium is a liquid, the fluid translation resulting from application of ultrasound is called acoustic streaming.

The ability of radiation force to concentrate microbubbles in-vitro and in-vivo has been demonstrated, e.g., Dayton, et al., *Ultrasound in Med. & Biol.*, 25(8):1195-1201(1999). An ultrasound transducer pulsing at 5 MHz center frequency, 10 kHz pulse

repetition frequency (“PRF”), and 800 kPa peak pressure, has been shown to concentrate microbubbles against a vessel wall in-vivo, and reduce the velocity of these flowing agents an order of magnitude. In addition, the application of radiation to concentrate drug delivery carrier particles and the combined effects of radiation force-induced concentration and carrier fragmentation has been demonstrated. See U.S. patent application Ser. No. 10/928,648, entitled “Ultrasonic Concentration of Drug Delivery Capsules,” filed Aug. 26, 2004 by Paul Dayton et al., which is incorporated herein by reference.

Acoustic streaming and optionally radiation force may be used to “push” or concentrate microbubbles injected into the tissue along a cell membrane. Notably, acoustic streaming has previously been used to push or concentrate carrier particles within a blood vessel. In contrast, the present invention utilizes acoustic streaming to push bubbles within subcutaneous tissue to concentrate the bubble against the walls of cells to be treated.

According to one aspect of the present invention, a solution containing microbubbles is injected into subcutaneous tissue or a solution containing dissolved gas is injected into subcutaneous tissue and insonated to bring the gas out of solution thereby generating bubbles within the subcutaneous tissue. The bubbles are pushed against the cell walls using acoustic streaming, and then insonated to induce transient cavitation to enhance the transport of the solution through the cell membrane and/or mechanically disrupt the cell membrane to selectively lyse cells.

The ultrasound parameters useful for inducing acoustic streaming include ultrasound waves having center frequencies about 0.1-20 MHz, at an acoustic pressure about 100 kPa-20 MPa, a long cycle length (e.g., about >10 cycles and continuous-wave) OR a short cycle length (e.g., about <10 cycle), and high pulse repetition frequency (e.g., about >500 Hz). The specific parameters will depend on the choice of carrier particle, as detailed further below, and can be readily determined by one of ordinary skill in the art.

According to one embodiment, the transducer apparatus 204 includes a single transducer capable of operating a plurality of operating modes to facilitate stable cavitation, transient cavitation, acoustic streaming, and sonoporation. According to another embodiment, the transducer apparatus 204 includes first and second transducers with first transducer optimized for popping bubbles (transient cavitation) and the second transducer optimized for bringing dissolved gas out of solution (stable cavitation) and/or pushing the bubbles using acoustic radiation force.

The transducer apparatus may produce focused, unfocused, or defocused ultrasound waves. Focused ultrasound refers to generally converging ultrasound waves, unfocused ultrasound refers to generally parallel ultrasound waves and defocused ultrasound wave refers to generally diverging ultrasound waves.

5 However, according to a preferred embodiment, the transducer apparatus 204 selectively produces unfocused and/or defocused ultrasound waves. For example, it may be desirable to utilize unfocused waves during transient cavitation, and defocused waves during stable cavitation. To this end the transducer apparatus may include a flat transducer, i.e., a transducer having a generally planar acoustic wear layer (acoustic
10 window) for producing unfocused ultrasound waves (nonconverging waves) and/or a convex transducer, i.e., a transducer having a convex acoustic wear layer for producing defocused ultrasound waves (diverging waves).

As will be appreciated by one of ordinary skill in the art, there are many different configurations for the ultrasound apparatus. FIG. 14 depicts an embodiment in which the
15 transducer apparatus 204 includes an inner transducer 204A and an outer transducer 204B. In the illustrated embodiment, the inner transducer 204A has a convex shaped acoustic wear layer for producing defocused waves 205A, and the outer transducer 204B has a planar shaped acoustic wear layer for producing unfocused waves 205B. However, both of the inner and outer transducers 204A and 204B may be planar or both may be convex.
20 Still further, one or both of the inner and outer transducers may be concave, i.e., may have a concave acoustic wear layer for producing focused waves. Thus, the ultrasound apparatus 204 may include any combination of focused, unfocused, and defocused transducers.

The inner and outer transducers depicted in FIG. 14 are both circular and the outer
25 transducer surrounds (encircles) the inner transducer. However, other configurations are contemplated and fall within the scope of the invention. According to a presently preferred embodiment, the inner transducer is used to produce stable cavitation and the outer transducer is used to create transient cavitation. However, the relative positions may be swapped with the inner transducer producing transient cavitation and the outer
30 transducer producing stable cavitation.

The ultrasound apparatus 204 illustrated in FIG. 14 includes a needle array 214 of the type described elsewhere in this disclosure. The transducer apparatus 204 of FIG. 14 may be incorporated in any of the embodiments disclosed herein which include an

ultrasound transducer. Notably, the transducer apparatus 204 may be incorporated in system 200.

It should be noted that the transducer apparatus 204 may include one or more arrays of transducers. For example, the transducer apparatus may include an array of
5 transducers for stable cavitation and/or an array of transducers for transient cavitation.

According to another aspect of the present invention, a solution which may or may not include microbubbles is injected into subcutaneous tissue. The solution is pushed against the cell walls using acoustic streaming, and then the subcutaneous tissue is insonated to induce sonoporation and facilitate the uptake/absorption of solution by the
10 tissue. Solution is injected and insonated using a system such as system 200 depicted in FIG. 13 which does not include a bubble generator 100. Absorption of the solution preferably results in cell lysis.

As described in U.S. Utility Patent Application Serial Number 11/292,950 filed December 2, 2005, the ultrasound energy from ultrasound generator 206 is applied to the
15 tissue 220 via ultrasound transducer 204. Ultrasound control unit 208 controls the various ultrasound parameters and generally controls the supply of ultrasound by generator 206. Preferably, ultrasound control unit 208 communicates with the injection control unit 210 to synchronize the application of ultrasound energy with the injection of fluid. It may for example be desirable to quickly apply energy to the tissue before the microbubbles
20 dissipate or are absorbed by the tissue.

The ultrasound transducer 204 is preferably configured to deliver unfocused ultrasound at an intensity and pressure sufficient to noninvasively cavitate the microbubbles within tissue thereby causing cell lysis. The intensity and pressure of the ultrasound applied to the tissue is preferably selected to minimize the heating of tissue and
25 in particular avoid burning the patient's skin. The transducer 204 may include a thermocouple 238 or the like to monitor the temperature of the transducer 204.

In at least one embodiment the liposculpture system 200 (FIG. 2) includes an ID reader 250 (shown in dashed lines), and the needle array 214 includes an identifier 252 (shown in dashed lines), which uniquely identifies the needle array 214. The ID reader
30 250 reads the identifier 252, and preferably authenticates or verifies the needle array 214. The identifier 252 may contain information identifying the characteristics of the needle array 214 such as length and gauge of needles. The identifier 252 may further include identifying information which may be used to track the number of injection cycles (needle deployments) or use time for a given array 214.

The reader 250 preferably communicates with the injection control unit 210. The injection control unit 210 may count the number of injection cycles that a given needle array 214 has been used, and may warn the operator if the number exceeds a threshold number. The injection control unit 250 may use information stored on the identifier 252 to
5 adjust the injection depth or injection flow rate. The injection control unit 210 may further inhibit usage of a needle array if it cannot authenticate, verify or read the identifier 252.

The identifier 252 may be a barcode label, a radio frequency tag, smart chip or other machine-readable medium such as known in the art.

The ultrasound transducer 204 may also include an identifier 252. The identifier
10 252 may be used to store information identifying the characteristics of the transducer 204, which is used by the ultrasound control unit 208 in setting or verifying the treatment settings. The ultrasound control unit 208 may inhibit insonation if it cannot authenticate, verify or read the identifier 252.

As described above, the transducer 204 may be integrated with the needle array
15 214 in which case a single identifier 252 may store information describing characteristics of both the needle(s) 218 and the transducer 204. The ultrasound control unit 208 may use information on the identifier 252 to track the amount of time the identified ultrasound transducer 204 has been operated and at what power levels, and may inhibit insonation if the accumulated insonation time exceeds a threshold value.

The constituent components of the device 100 may be formed of any sterilizable,
20 biocompatible material. Moreover, some or all of the components may be disposable, i.e., manufactured for single-patient use, to minimize potential cross-contamination of patients. The needle array 214 is preferably a disposable component, as the needles 218 will likely dull with use.

One or more optical or pressure sensors 254 (FIG. 5) may be provided to measure
25 pressure exerted on the handpiece 300 (FIG. 12A) when the handpiece is placed in abutment with the tissue. The pressure sensor(s) 254 may provide a safety interlock function to prevent inadvertent deployment of the needle array 214 and/or actuation of the transducer 204 unless pressure is detected as the handpiece 300 is placed in abutment with
30 the tissue. If two or more pressure sensors 254 are provided the injection of solution and/or insonation may be inhibited unless each of the measured pressure values fall within a predefined window and/or so long as the difference between any given two measured pressure values is less than a threshold value. The pressure sensor(s) 254 may, for example, be provided on the needle array 214 (FIG. 4) or on the fluid injection device 202

(not illustrated). Alternatively, other sensing means, possibly optical or capacitive, may be used to detect proper positioning of the needle array against the tissue to be treated.

It may be advantageous to couple the needles 218 with the ultrasound transducer 204 such that ultrasound is transmitted through the needle(s) 218 to the tissue. Applying
5 ultrasound in this manner may facilitate targeted cavitation and/or may facilitate penetration of the needle(s) 218 into the tissue.

FIG. 13 is a block diagram of a system 200 for a fat lysing system according to the present invention. The system 200 is identical to the system 200 of FIG. 2 but excludes the bubble generator 100. Moreover, the ultrasound transducer 204, ultrasound generator
10 206, and ultrasound control unit 208 are shown in dashed lines to indicate that these are optional components. The system 500 may be used to inject a fat lysing solution (as will be described below in greater detail) with or without the use of ultrasound.

According to one embodiment, the fat lysing solution includes epinephrine as its active ingredient. The epinephrine may be combined with an aqueous solution, isotonic
15 saline, normal saline, hypotonic saline, hypotonic solution, or a hypertonic solution. The solution may optionally include one or more additives/agents to raise the pH (e.g., sodium bicarbonate) or a buffering agent such those listed in Table 5 above or other buffering agents such as known in the art.

According to a presently preferred embodiment the fat lysing solution includes
20 epinephrine in hypotonic buffered saline.

The inclusion of ultrasound in system 200 may facilitate the absorption and/or distribution of the fat lysing solution. The inclusion of ultrasound in system 200 may facilitate the absorption and/or distribution of the fat lysing solution. More particularly,
25 the ultrasound may be used to enhance the distribution, absorption, and/or uptake of the solution in the tissue by permanently or temporarily opening pores in the cell membrane (sonoporation), generating microstreaming in the solution, or locally heating the solution or the tissue. According to one aspect of the invention, the ultrasound generator 206 may be operated at a first setting to facilitate distribution of the solution and then it may be operated at a second setting to facilitate absorption. The sonoporation may be reversible or
30 irreversible.

The system 200 may include an optional ultrasound transducer 258 for vibrating the needles 218 to facilitate tissue penetration and/or a needle rotation mechanism 256 which may be used in conjunction with side-firing needles 218 to facilitate even distribution of the solution. The same transducer apparatus 204 used to facilitate

absorption and/or distribution of the solution may be used to facilitate tissue penetration thereby eliminating the need for a separate transducer 258.

The system 200 may include any or all of the features described in this disclosure including means for selectively adjusting the amount of solution injected by each of the
5 needles 218 and/or the rate or pressure at which the solution is injected into the tissue. Still further the system 200 may include the selective adjustment of the injection depth and/or the tissue apposition mechanism as described above.

Mode of Operation/ Method of Use

According to a first mode of operation, solution is percutaneously injected into
10 subcutaneous tissue, and the tissue is insonated at a first ultrasound setting to distribute the solution. Once the solution has been distributed the tissue is insonated at a second setting to induce sonoporation thereby inducing cell lysis. According to this mode of operation the solution need not contain microbubbles as they do not contribute to cell lysis. To increase the efficacy of this mode of operation it is recommended to repeat the injection
15 and insonation of the tissue through 10 to 50 cycles.

According to a second mode of operation, a solution containing microbubbles is percutaneously injected into subcutaneous tissue, and the tissue is insonated at a first ultrasound setting to distribute the solution and/or push the microbubbles against the cell
20 walls. Thereafter the tissue is insonated at a second setting (for between 1 millisecond and 1 second) to induce transient cavitation inducing cell lysis. To increase the efficacy of this mode of operation it is recommended to repeat the injection and insonation of the tissue through 10 to 50 cycles.

It should be appreciated that it is important to synchronize the timing of the insonation. Notably, the microbubbles will be absorbed by the tissue and/or go into
25 solution within a relatively short period of time. Thus, it is important to distribute the microbubbles (using acoustic radiation force) and induce transient cavitation within a relatively short time after the solution has been injected into the subcutaneous tissue.

According to a presently preferred embodiment, the tissue is insonated to facilitate distribution of the microbubble solution through acoustic radiation force and/or
30 microstreaming occurs simultaneously as the solution is injected into the tissue or within a very short amount of time afterward. The injection of a small amount of the microbubble solution takes approximately 200 milliseconds and insonation to induce distribution through acoustic radiation force takes between 1 millisecond and 1 second. Next, the tissue is insonated to induce transient cavitation for approximately 400 milliseconds.

According to a third mode of operation, a solution containing dissolved gas, i.e., dissolved gas bubbles is percutaneously injected into subcutaneous tissue, and the tissue is insonated at a first ultrasound setting to bring the bubbles out of solution (for between 100 microseconds and 1 millisecond) followed immediately by insonation at a second setting
5 (for between 1 millisecond and 1 second) to distribute the solution and/or push the microbubbles against the cell walls. Thereafter the tissue is insonated at a third setting (for between 100 microseconds and 1 second) to induce transient cavitation inducing cell lysis. To increase the efficacy of this mode of operation it is recommended to repeat the injection and insonation of the tissue through 10 to 50 cycles.

10 It should be appreciated that it is important to synchronize the timing of the insonation. Notably, the microbubbles will be absorbed by the tissue and/or go into solution within a relatively short period of time. Thus, it is important to distribute the microbubbles (using acoustic radiation force) and induce transient cavitation within a relatively short time after the bubbles have been brought out of solution.

15 According to a presently preferred embodiment, the tissue is insonated to induce stable cavitation and bring the bubbles out of solution after the solution has been injected into the subcutaneous tissue. Satisfactory stable cavitation results have been achieved by insonating for approximately 100 microseconds. Thereafter the tissue is insonated to facilitate distribution of the microbubble solution through acoustic radiation force and/or
20 microstreaming occurs. Insonating for between 1 millisecond and 1 second is required to distribute the microbubbles. Immediately thereafter the tissue is insonated to induce transient cavitation for approximately 400 milliseconds.

The invention may be combined with other methods or apparatus for treating tissues. For example, the invention may also include use of skin tightening procedures, for
25 example, ThermaCool™ available from Thermage Corporation located in Hayward, California, Cutera Titan™ available from Cutera, Inc. located in Brisbane, California, or Aluma™ available from Lumenis, Inc. located in Santa Clara, California.

The invention may be embodied in other forms without departure from the spirit and essential characteristics thereof. The embodiments described therefore are to be
30 considered in all respects as illustrative and not restrictive. Although the present invention has been described in terms of certain preferred embodiments, other embodiments that are apparent to those of ordinary skill in the art are also within the scope of the invention. Accordingly, the scope of the invention is intended to be defined only by reference to the appended claims.

What is claimed is:

1. A system comprising:

a container containing a measured amount of a solution including at least one of a vasoconstrictor, a surfactant, and an anesthetic, said solution comprising a liquid and at

5 least one of a gas and a fluid;

a needle array in fluid connection with said container, said needle array including at least one needle.

2. The system according to claim 1, wherein the gas is at least partially dissolved in said fluid.

10 3. The system of claim 1, wherein the gas is fully dissolved in said liquid.

4. The system according to claim 3, wherein the container is enclosed, and the solution is maintained at greater than atmospheric pressure.

5. The system of claim 1, said at least one needle includes a lumen having a textured surface promoting the generation of microbubbles.

15 6. The system according to claim 2, wherein the gas comprises at least one gas selected from the group (air, oxygen, carbon dioxide, carbon dioxide, perfluoropropane, argon, hydrogen, Halothane, Desflurane, Sevoflurane, Isoflurane, and Enflurane).

7. The system according to claim 1, wherein the vasoconstrictor includes at least one of Norepinephrine, Epinephrine, Angiotensin II, Vasopressin and Endothelin.

20 8. The system according to claim 1, further comprising refrigeration means for maintaining the container at a predefined temperature range.

9. The system according to claim 1, wherein said container is thermally insulated.

10. The system according to claim 3, further comprising:

25 an ultrasound transducer apparatus capable of operating in at least one of first, second, third, and fourth energy settings,

wherein said first energy setting is selected to facilitate the absorption of solution by the tissue, said second energy setting is selected to facilitate stable cavitation, said third energy setting is selected to facilitate transient cavitation, and said fourth frequency range is selected to facilitate pushing bubbles within tissue.

30 11. The system of claim 10, wherein the transducer apparatus includes at least first and second transducers, wherein said first transducer facilitates popping of bubbles and said second transducer facilitates bringing dissolved gas out of solution.

12. The system of claim 11, wherein the first transducer surrounds the second transducer.

13. The system of claim 11, wherein the second transducer surrounds the first transducer.

14. The system of claim 11, wherein said transducer apparatus produces at least
5 one of unfocussed and defocused ultrasound waves.

15. The system of claim 11, wherein said transducer apparatus selectively produces nonfocused ultrasound waves in a first mode and defocused ultrasound waves in a second mode.

16. The system of claim 11, wherein said first transducer has a generally planar
10 acoustic wear layer and said second transducer has a convex acoustic wear layer.

17. The system of claim 10, wherein the transducer apparatus includes an array of first and second transducers, wherein said array of first transducers facilitates transient cavitation and than said array of second transducers facilitates bringing dissolved gas out of solution.

18. The system according to claim 10 which the transducer apparatus is
15 operably connected to the needle array.

19. The system according to claim 1 wherein the container is a cartridge containing a predetermined amount of solution.

20. A system comprising:
20 a container;
an aqueous solution in said container, said solution including epinephrine;
a needle array in fluid connection with said container and configured to percutaneously inject the solution into subcutaneous tissue, said needle array including at least one needle;
25 an ultrasound transducer apparatus capable of delivering ultrasound energy to the subcutaneous tissue at a frequency range selected to facilitate the absorption and/or uptake of solution by the tissue.

21. The system of claim 20, wherein said aqueous solution includes saline.

22. The system of claim 20, wherein the solution includes buffered saline.

23. The system of claim 20, wherein the solution includes buffered isotonic
30 saline.

24. A method for selectively lysing cells, comprising:
percutaneously injecting a solution including at least one of a vasoconstrictor, a surfactant, and an anesthetic into subcutaneous tissue,

insonating the tissue with ultrasound setting to distribute the solution by acoustic radiation force;

insonating the tissue at a second ultrasound setting to induce cell uptake of the solution.

5 25. A method for selectively lysing cells, comprising:
 percutaneously injecting a microbubble solution into subcutaneous tissue;
 insonating the tissue at a first ultrasound setting to distribute the solution
and push the microbubble against walls of the cells by acoustic radiation force;
 insonating the tissue at a second ultrasound setting to induce transient
10 cavitation.

 26. The method of claim 25, wherein the solution includes at least one of a vasoconstrictor, a surfactant, and an anesthetic.

 27. A method for selectively lysing cells, comprising:
 percutaneously injecting a solution into subcutaneous tissue, said solution
15 containing at least one of a dissolved gas and a partially dissolved gas;
 insonating the tissue to induce stable cavitation and generate microbubbles;
 insonating the tissue with ultrasound to distribute the solution and push the
microbubble against walls of the cells by acoustic radiation force;
 insonating the tissue with ultrasound to induce transient cavitation.

20 28. The method of claim 27, wherein the solution includes at least one of a vasoconstrictor, a surfactant, and an anesthetic.

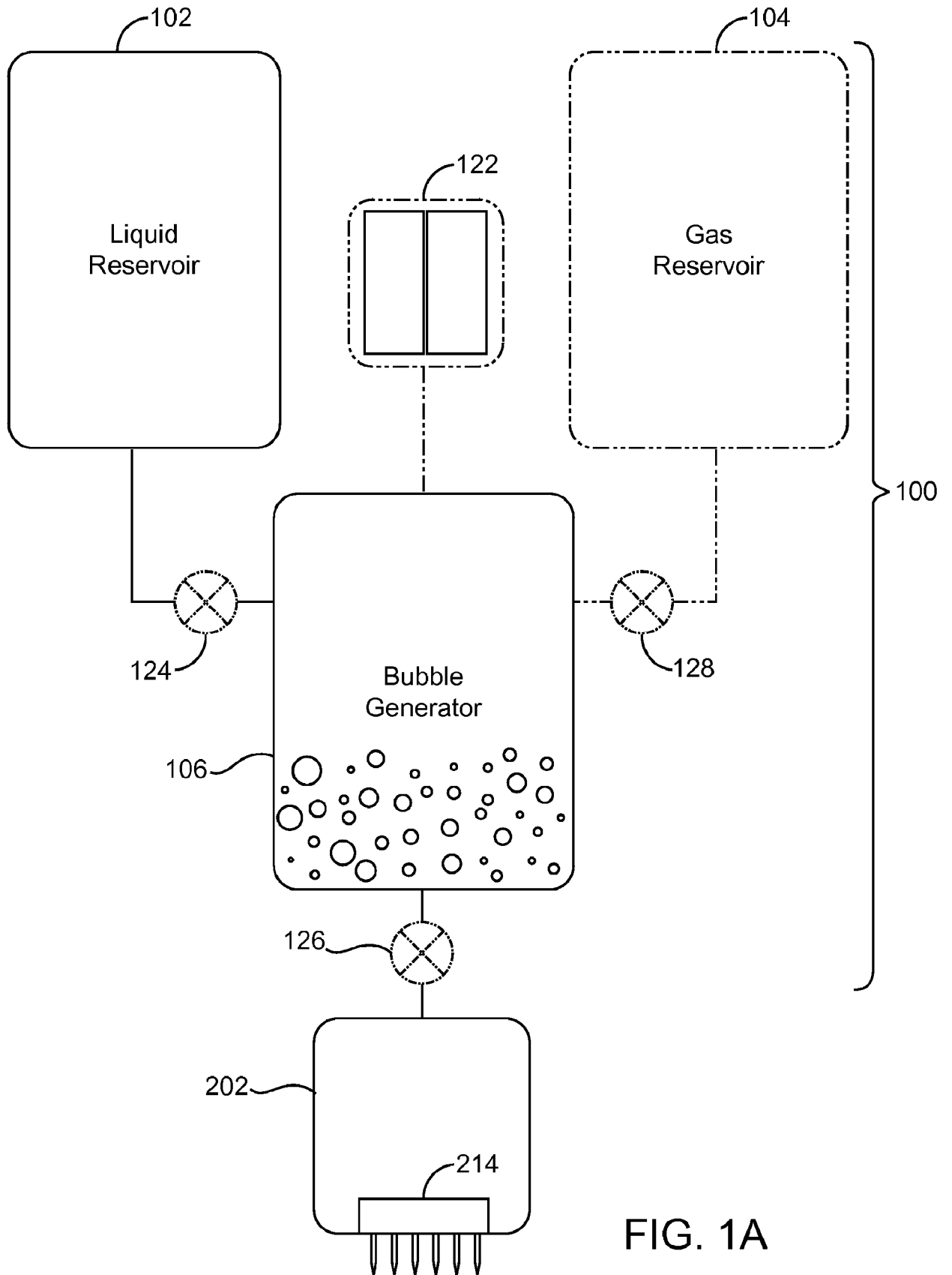


FIG. 1A

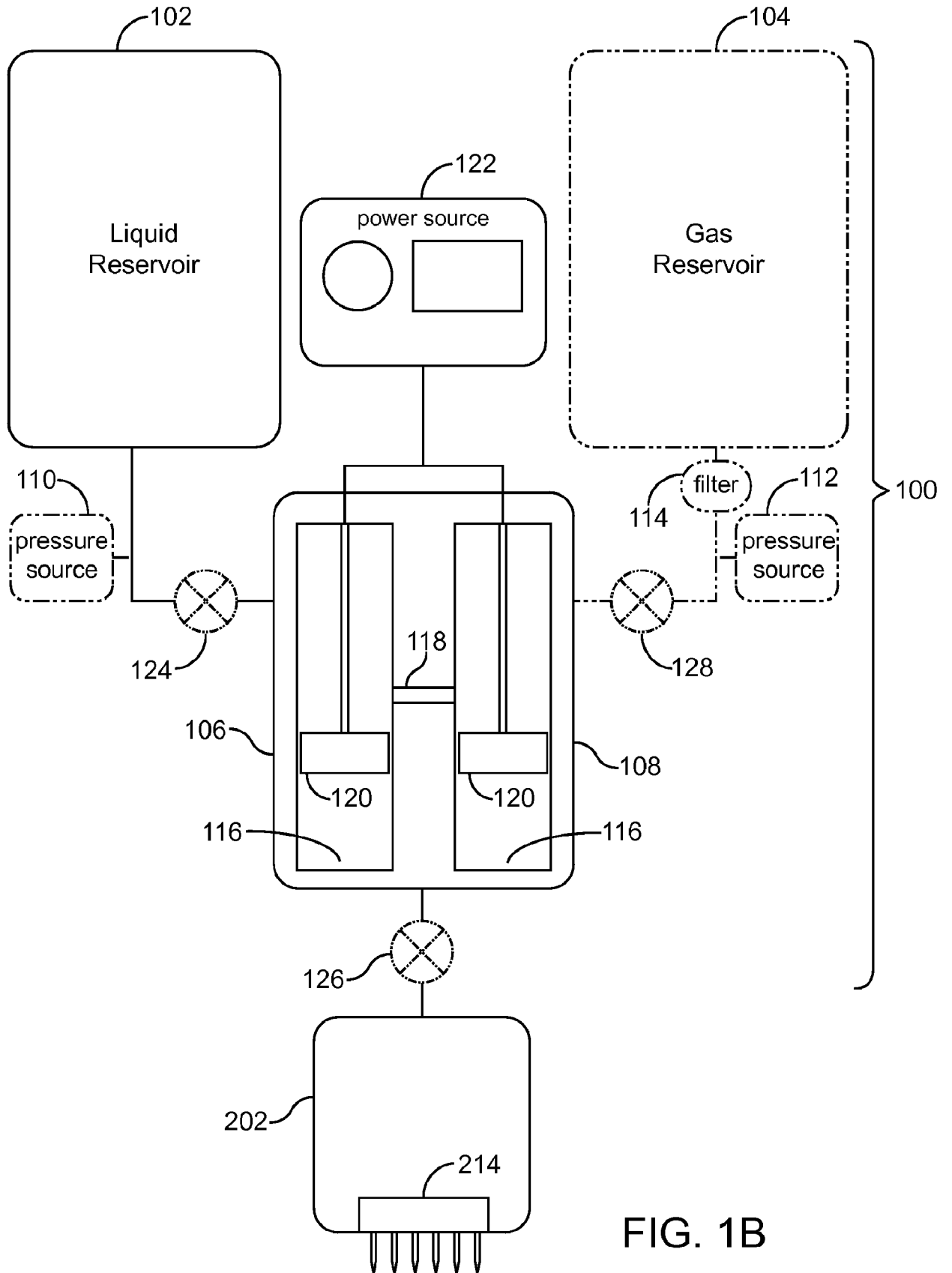


FIG. 1B

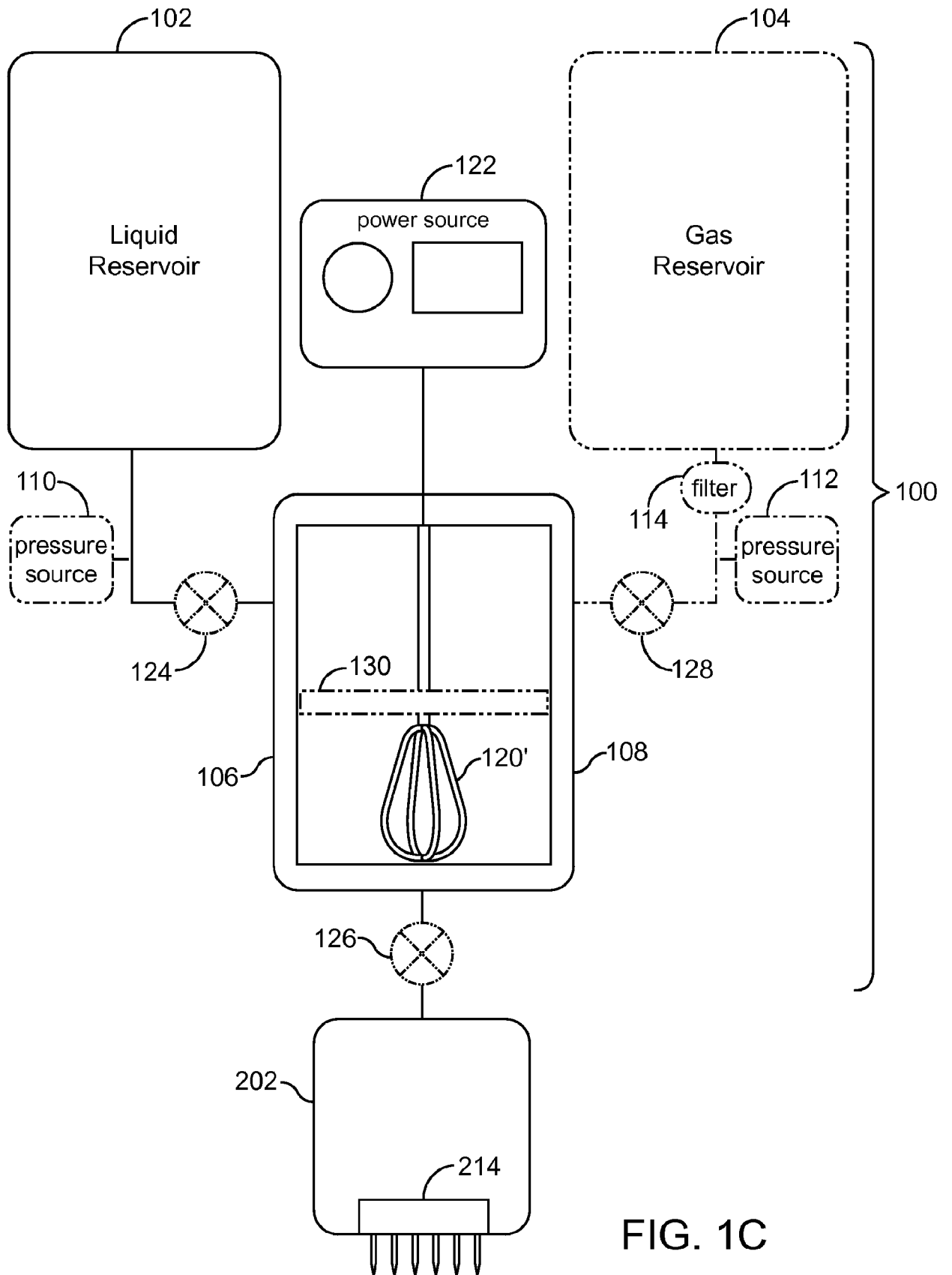


FIG. 1C

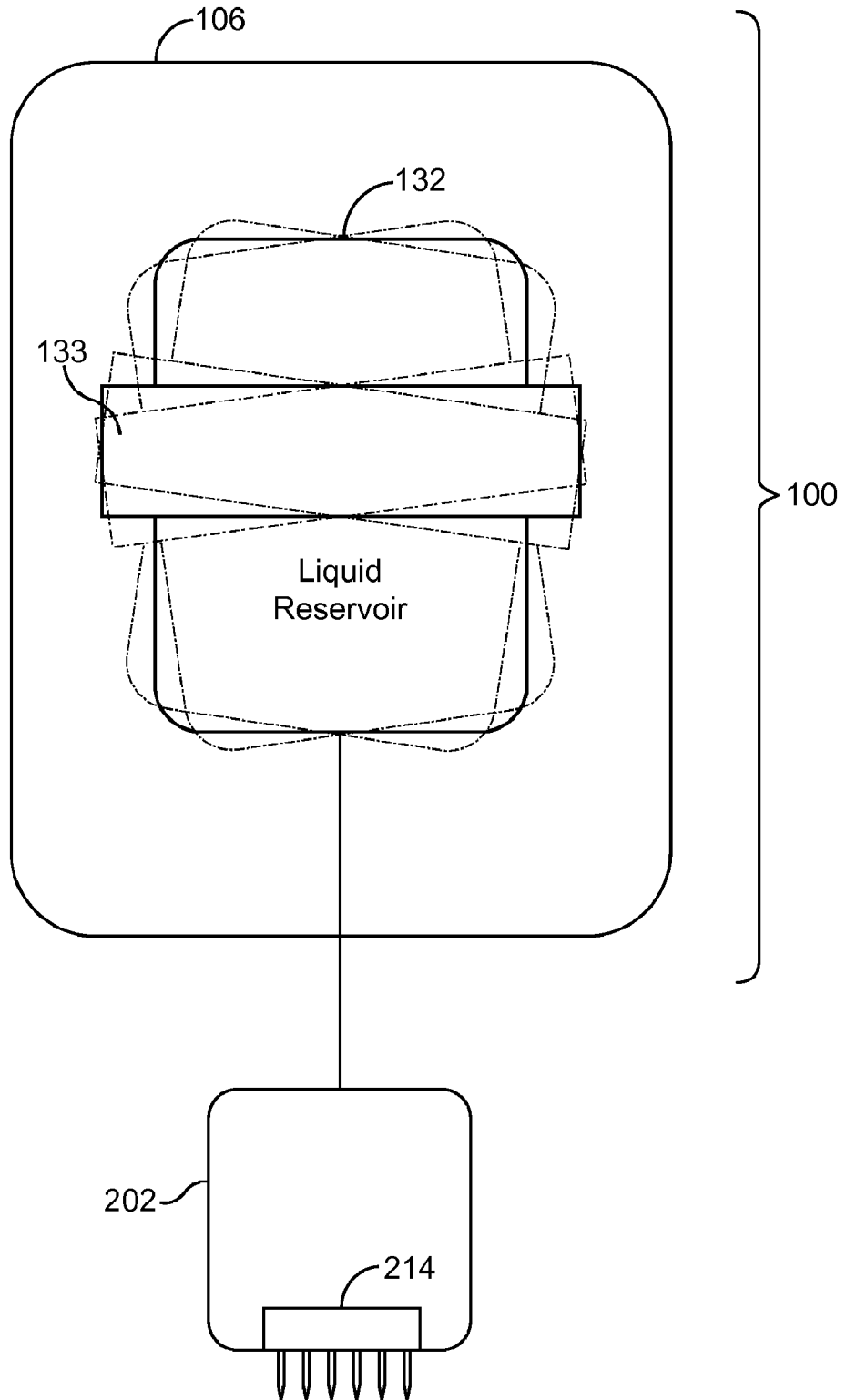


FIG. 1D

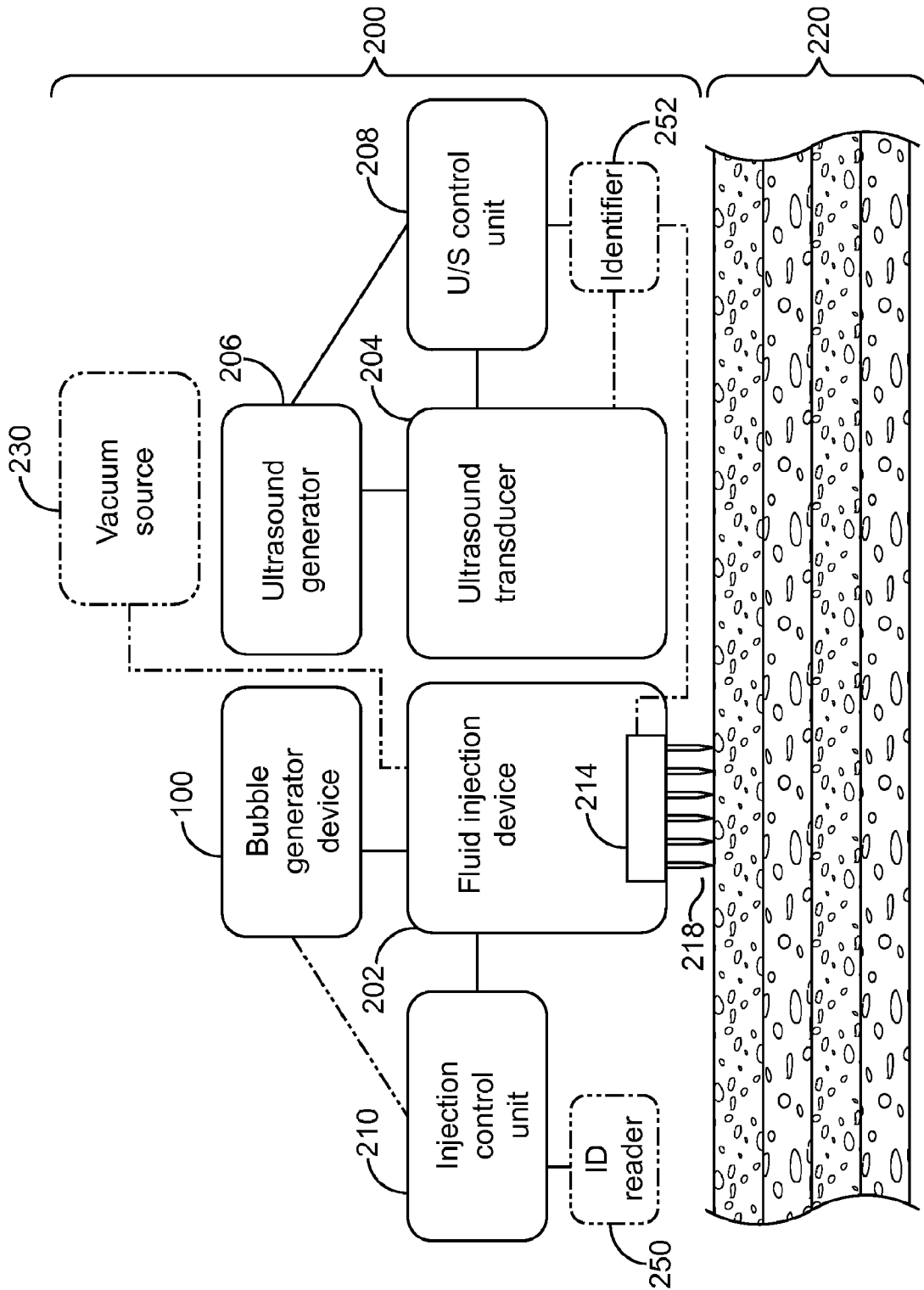


FIG. 2

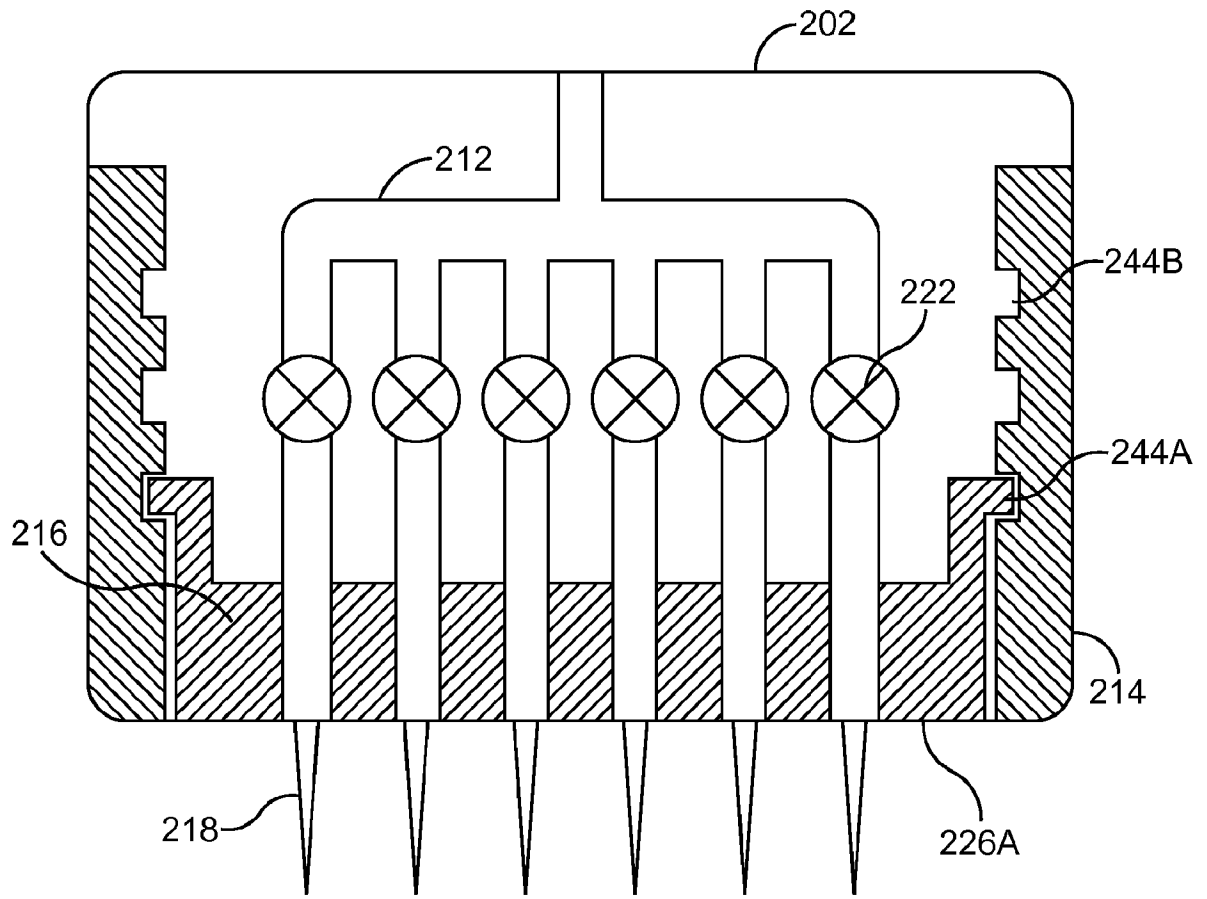


FIG. 3A

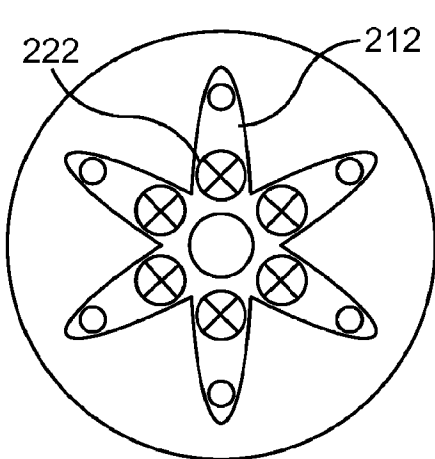


FIG. 3B

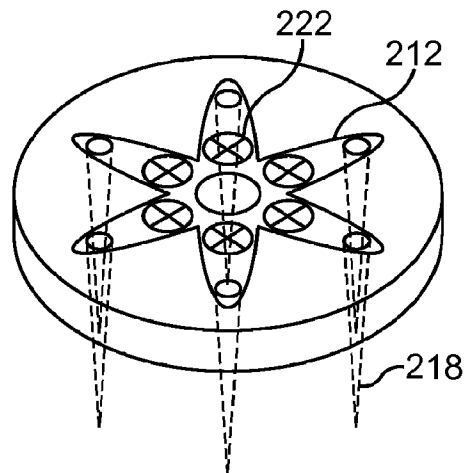


FIG. 3C

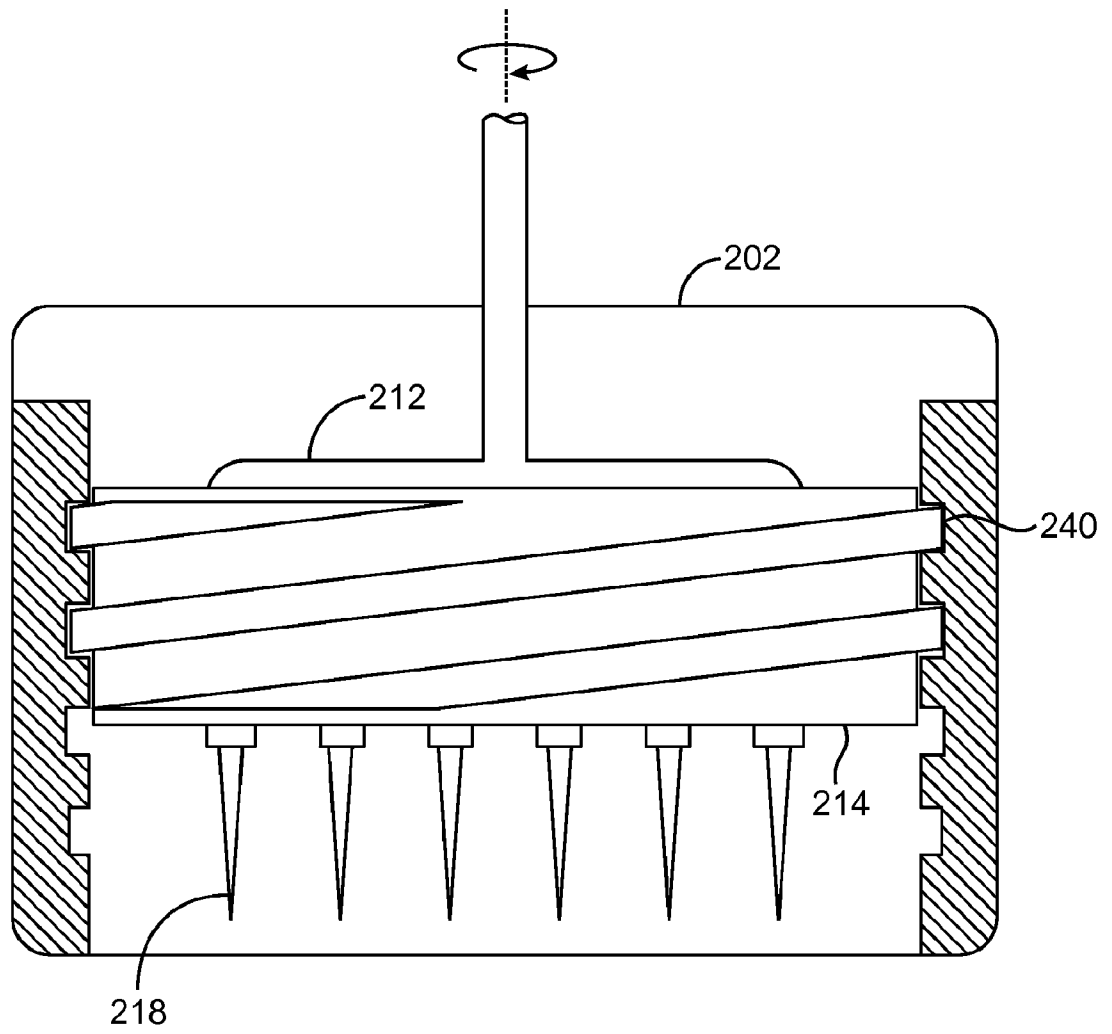


FIG. 3D

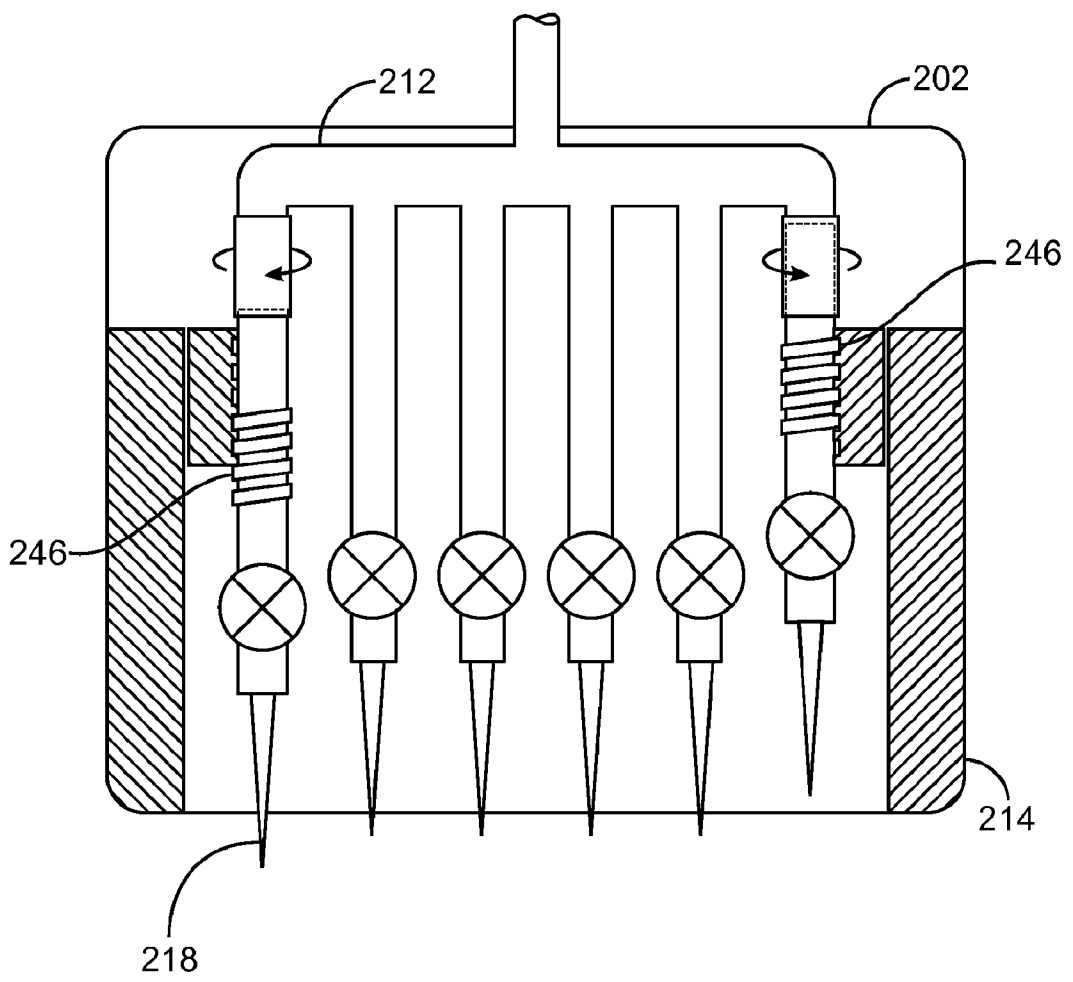


FIG. 4A

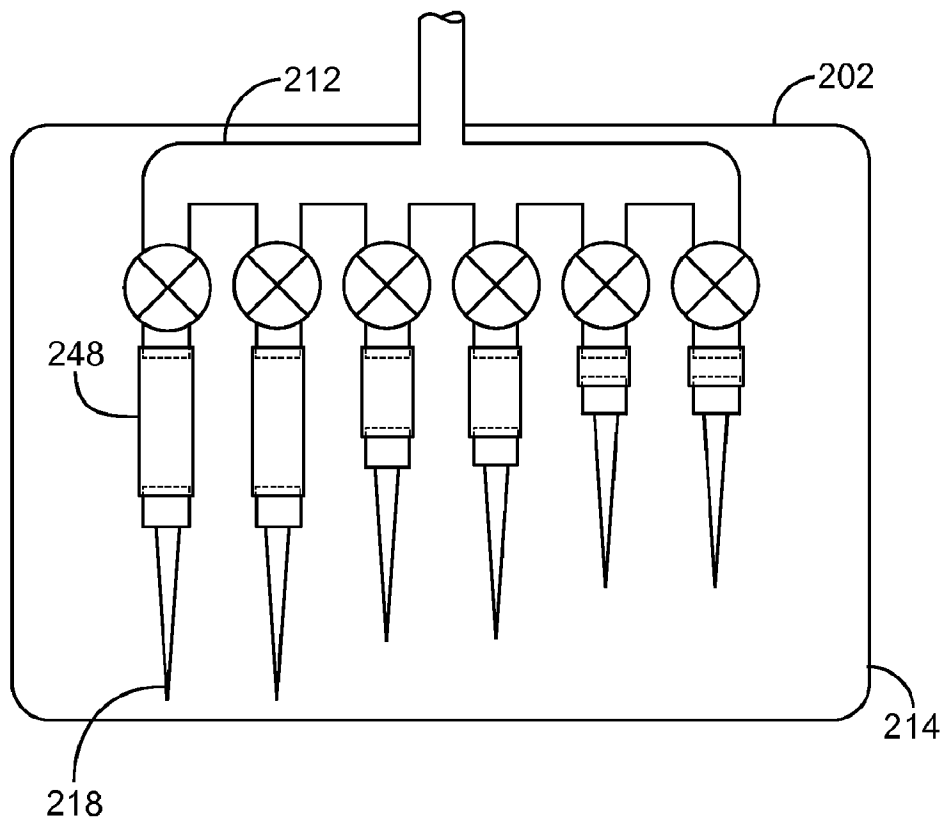


FIG. 4B

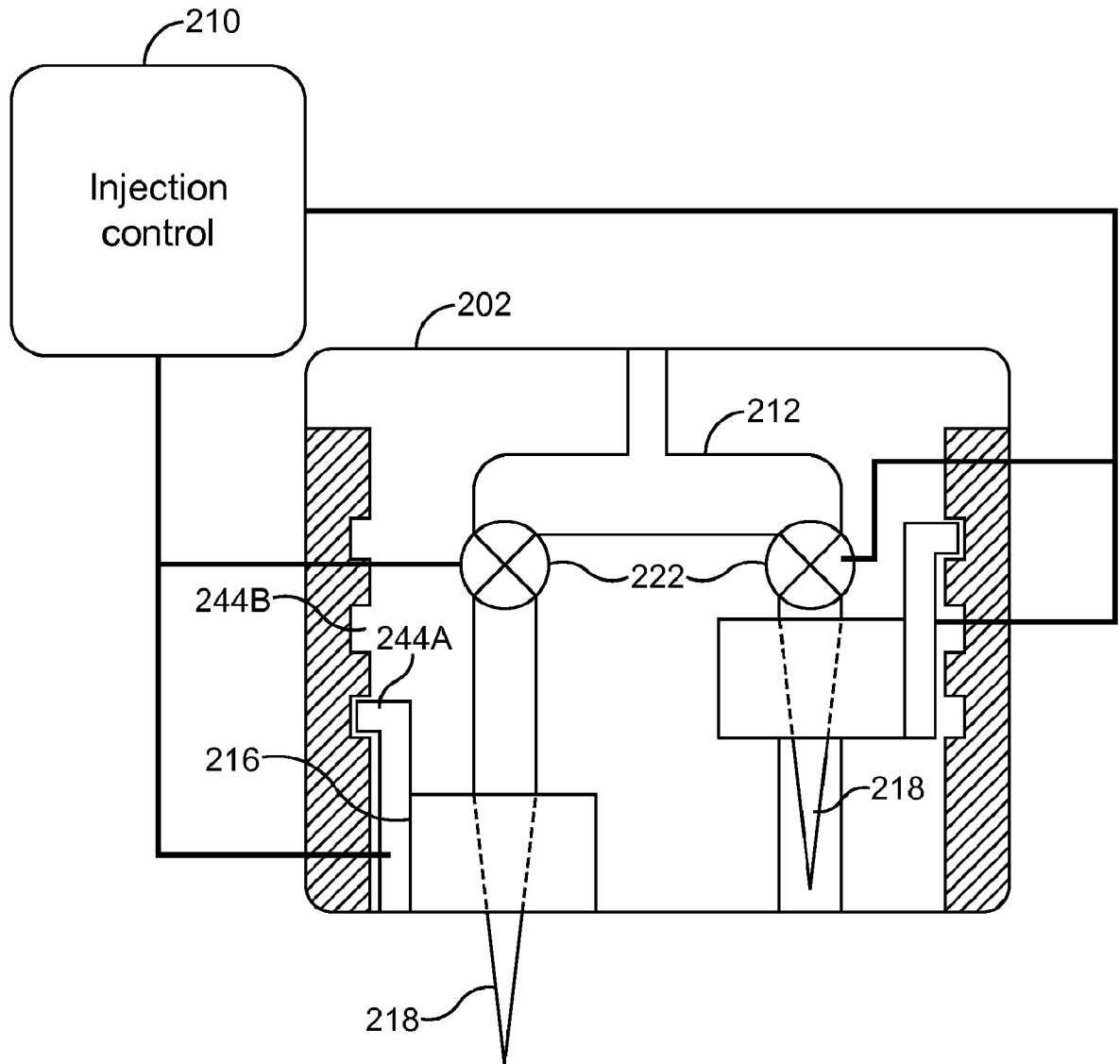


FIG. 4C

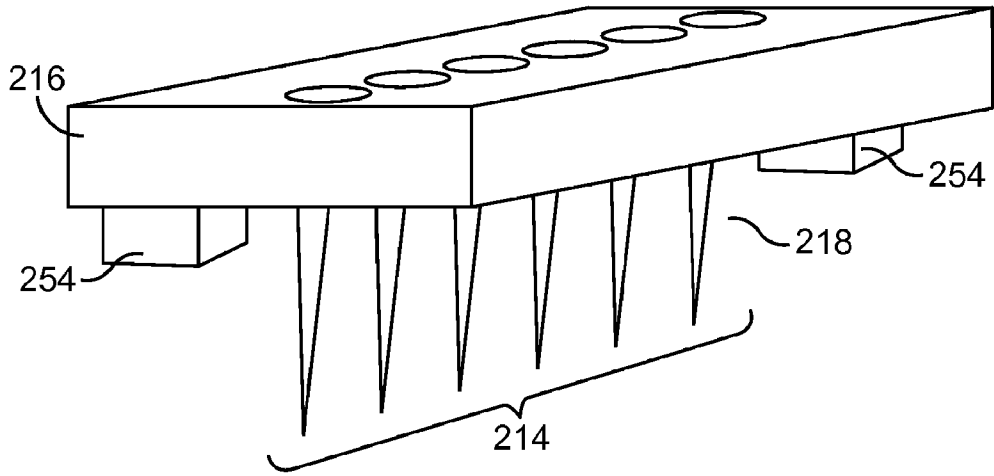


FIG. 5

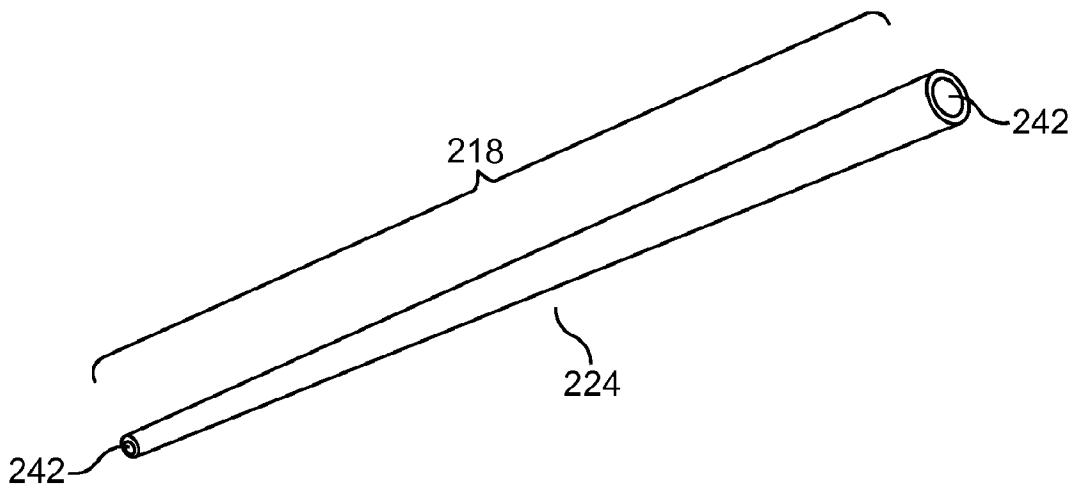


FIG. 6A

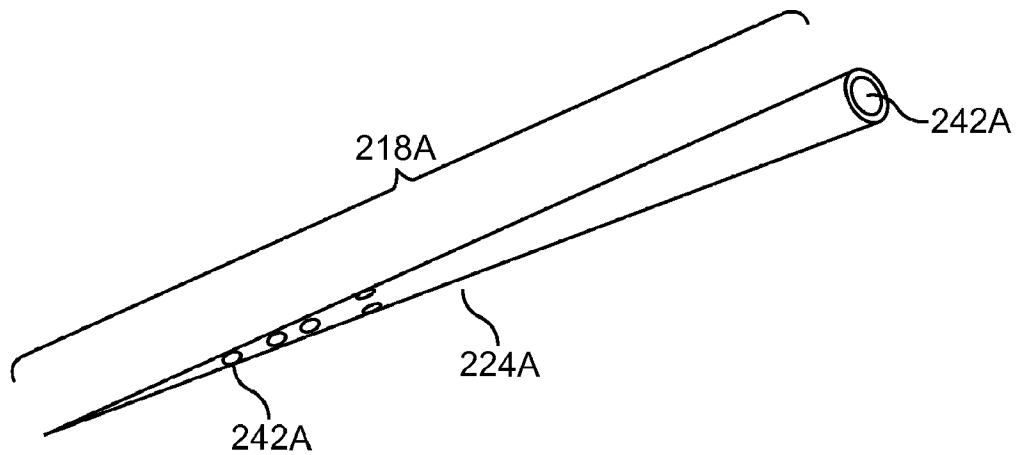


FIG. 6B

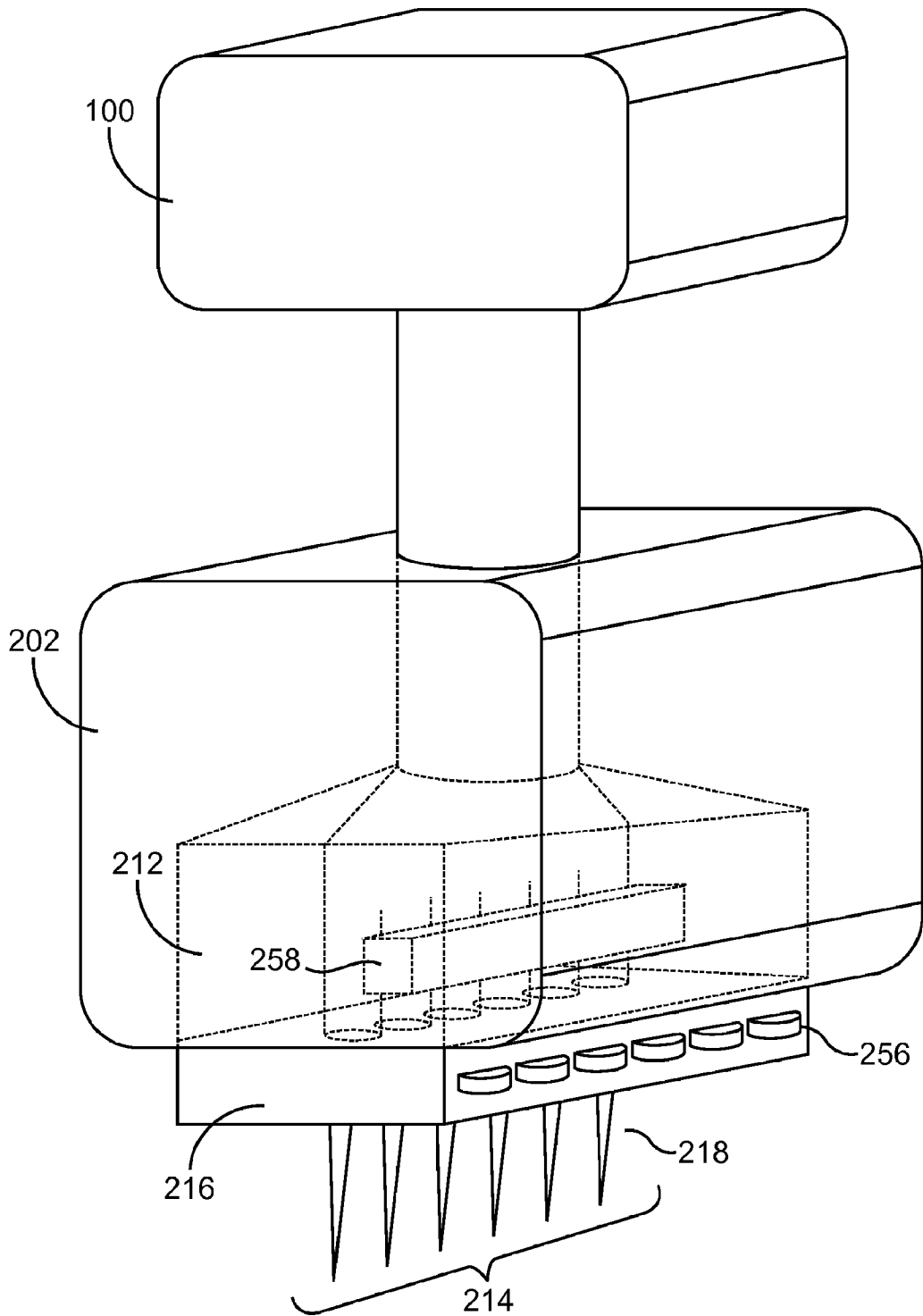


FIG. 7

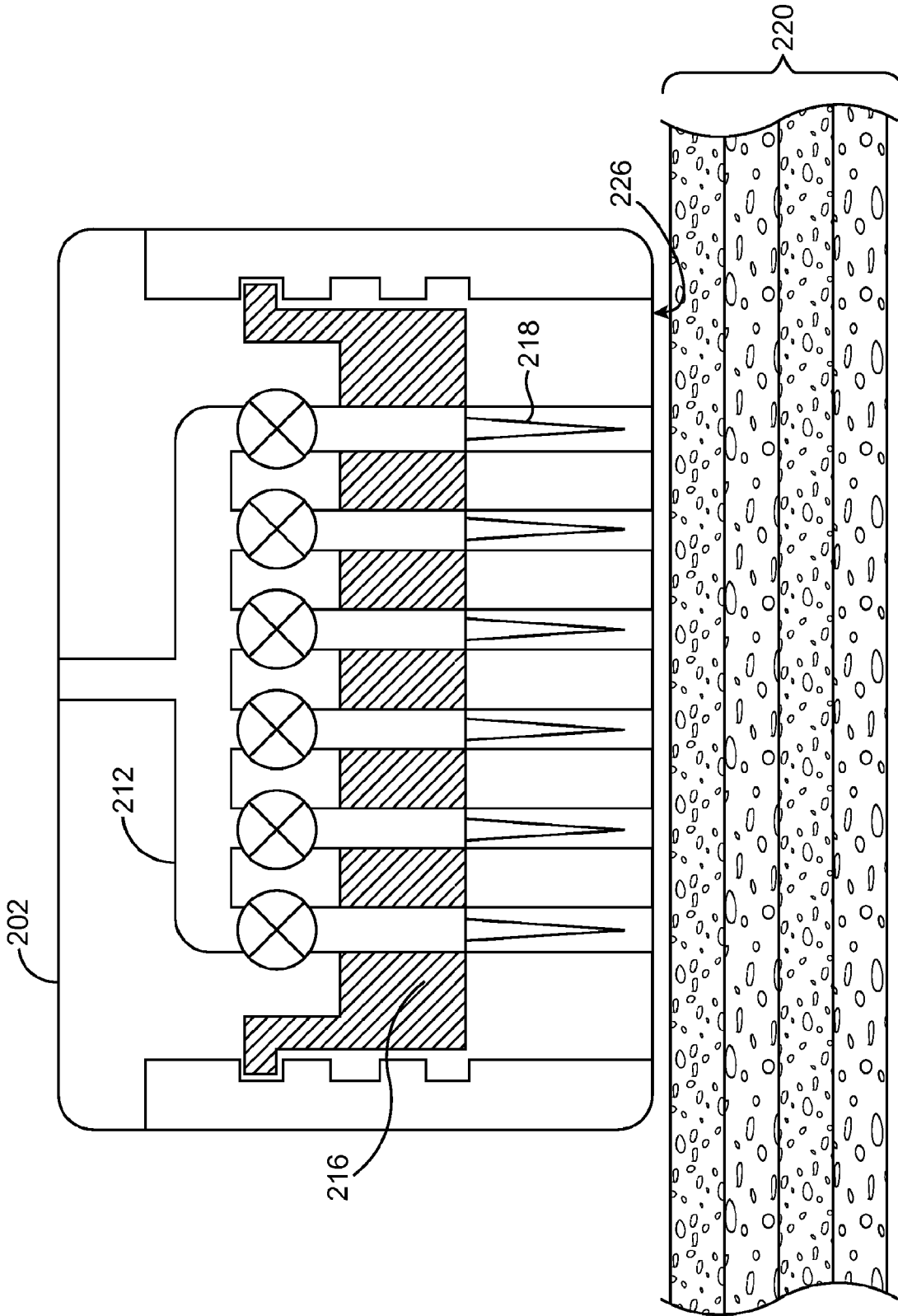


FIG. 8A

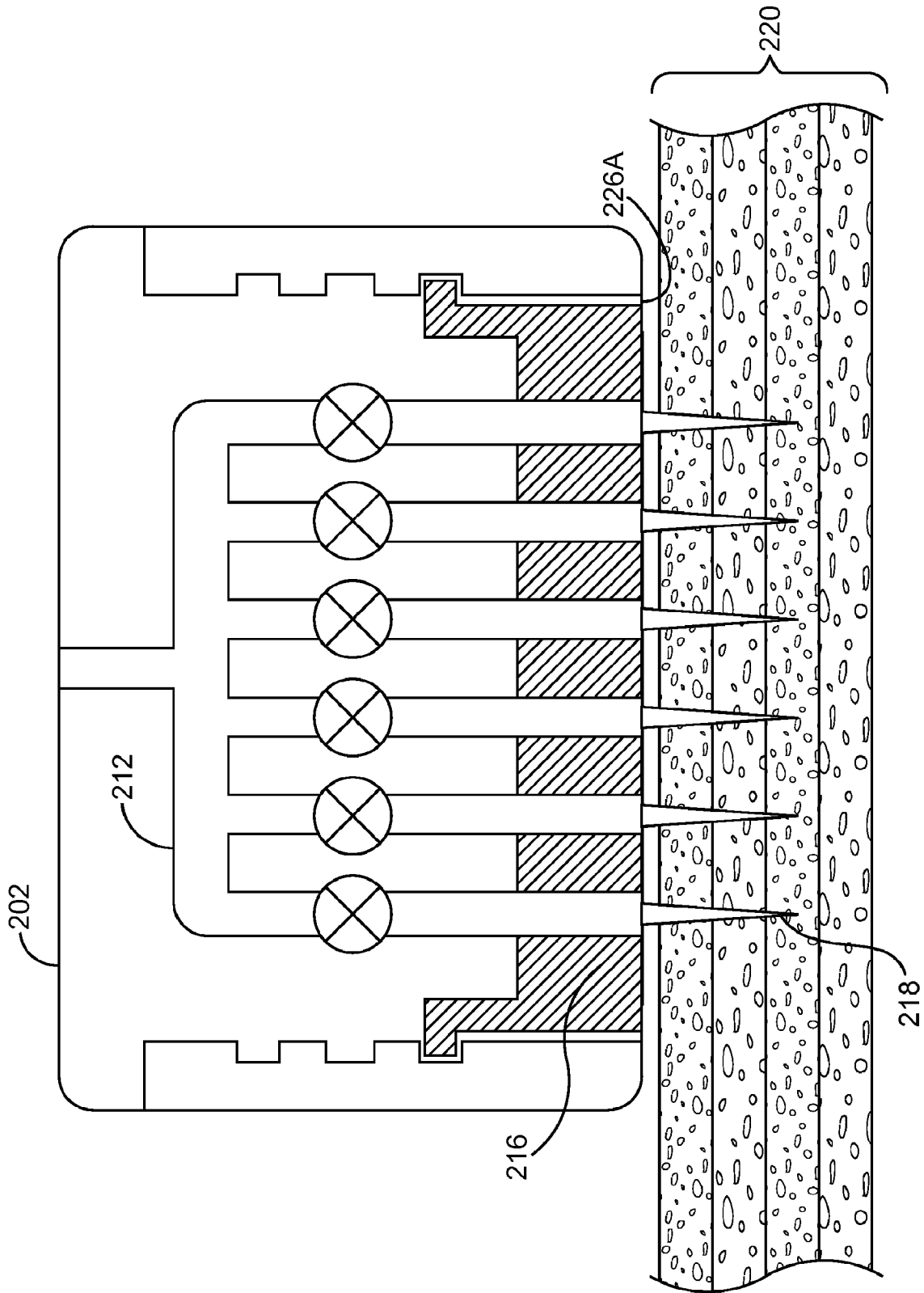


FIG. 8B

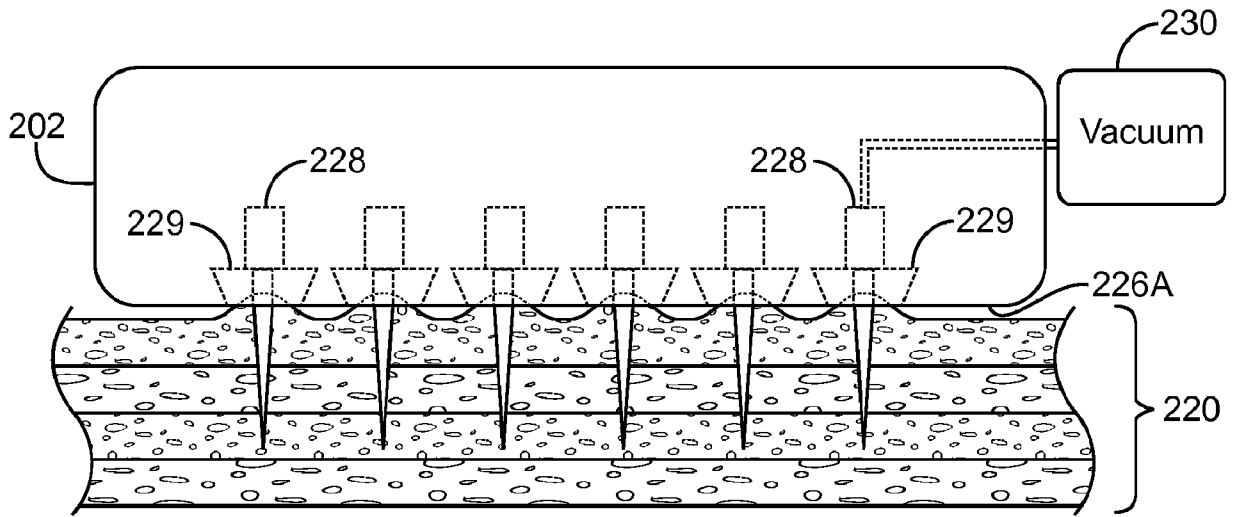


FIG. 9A

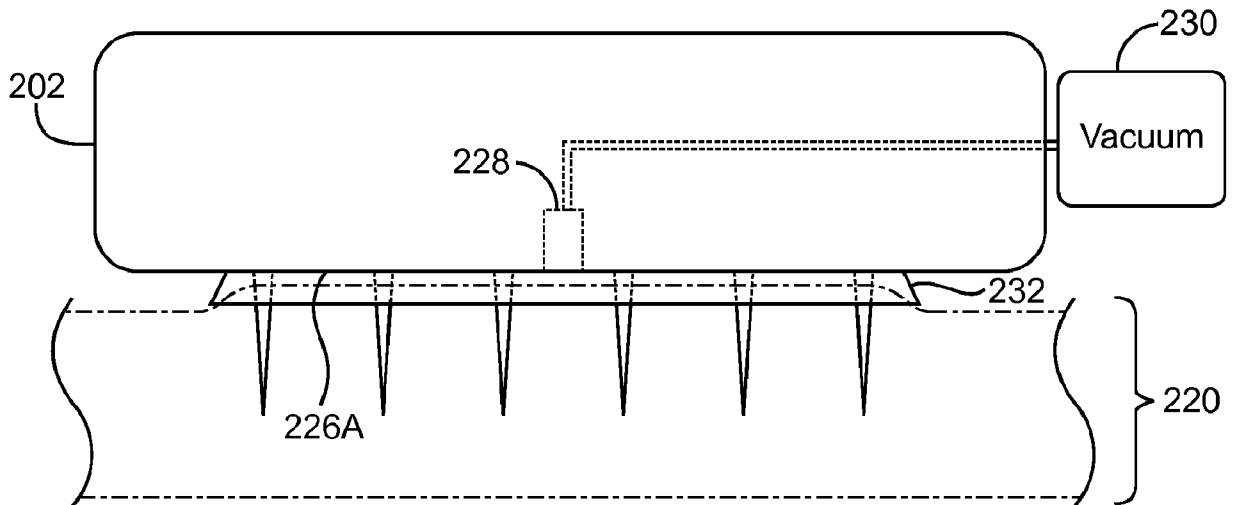


FIG. 9B

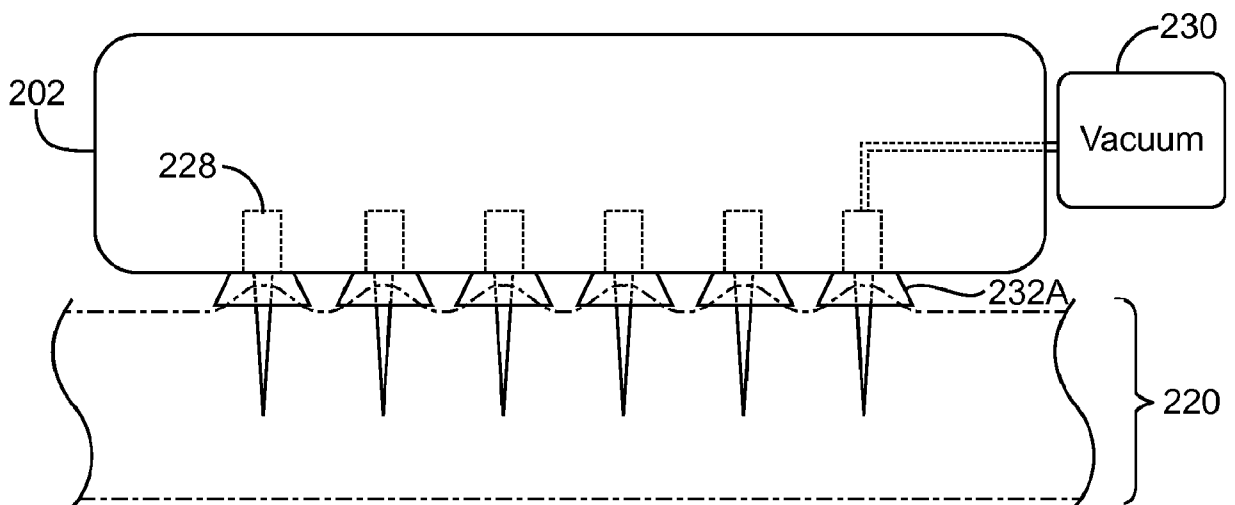


FIG. 9C

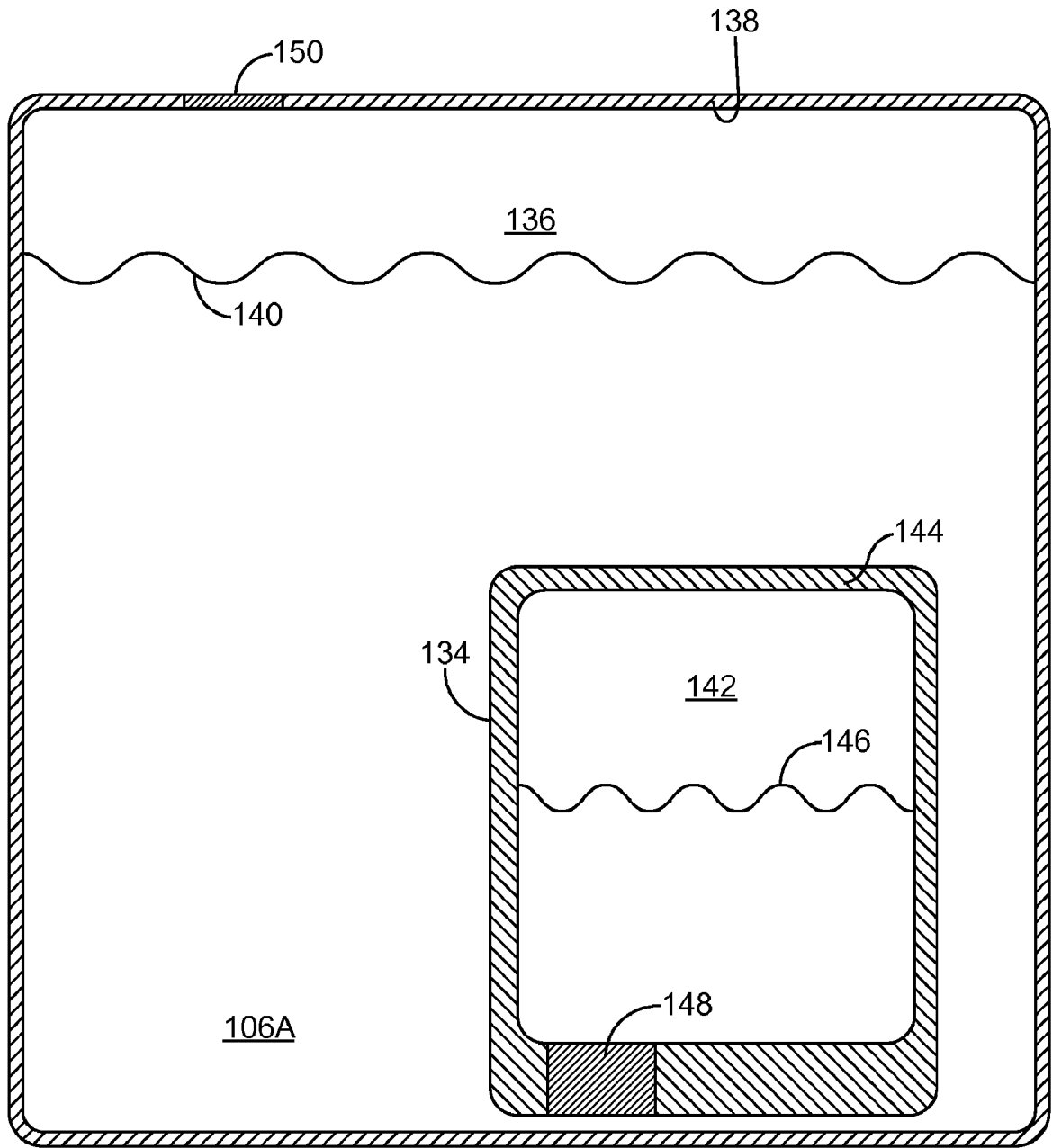


FIG. 10A

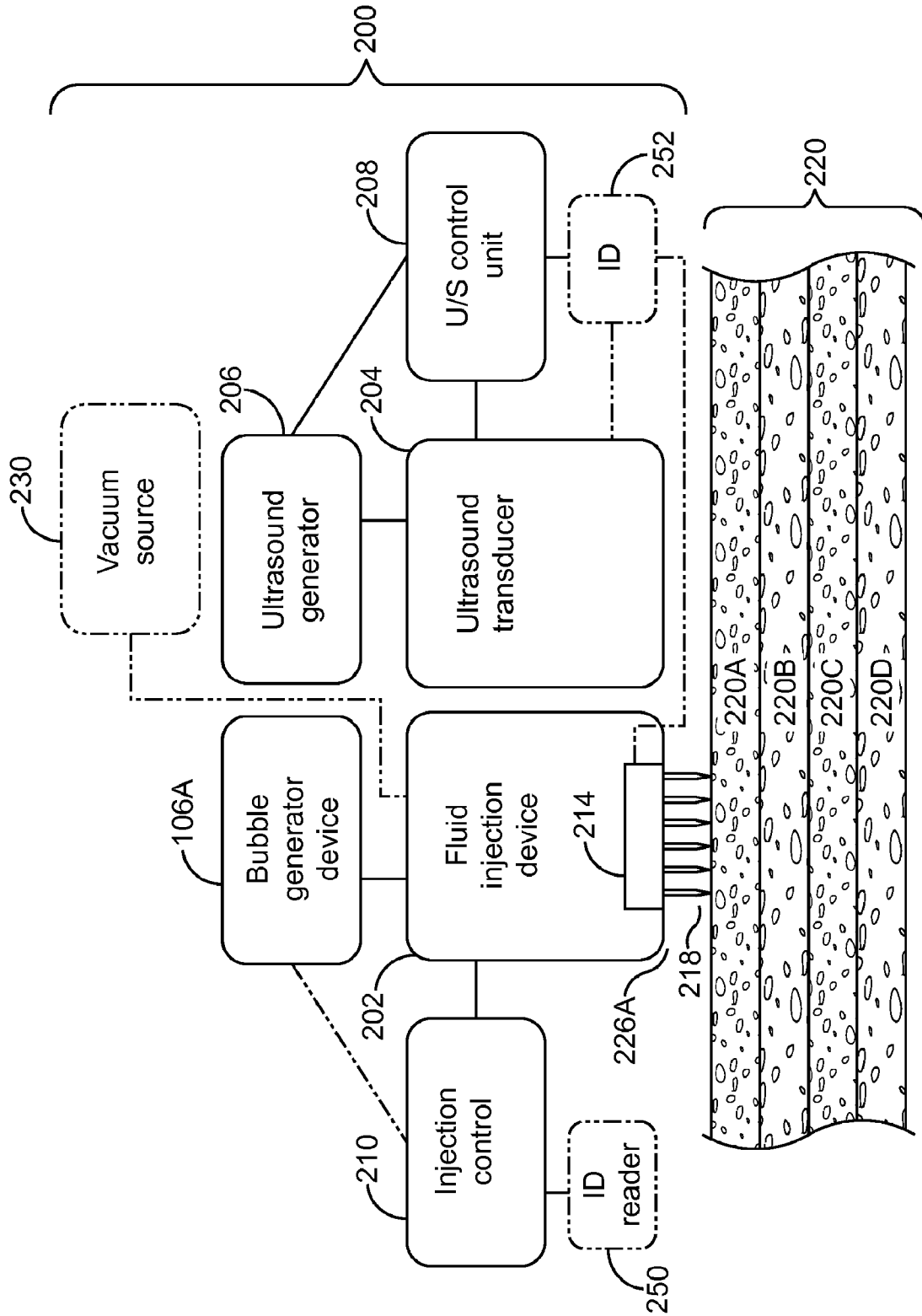
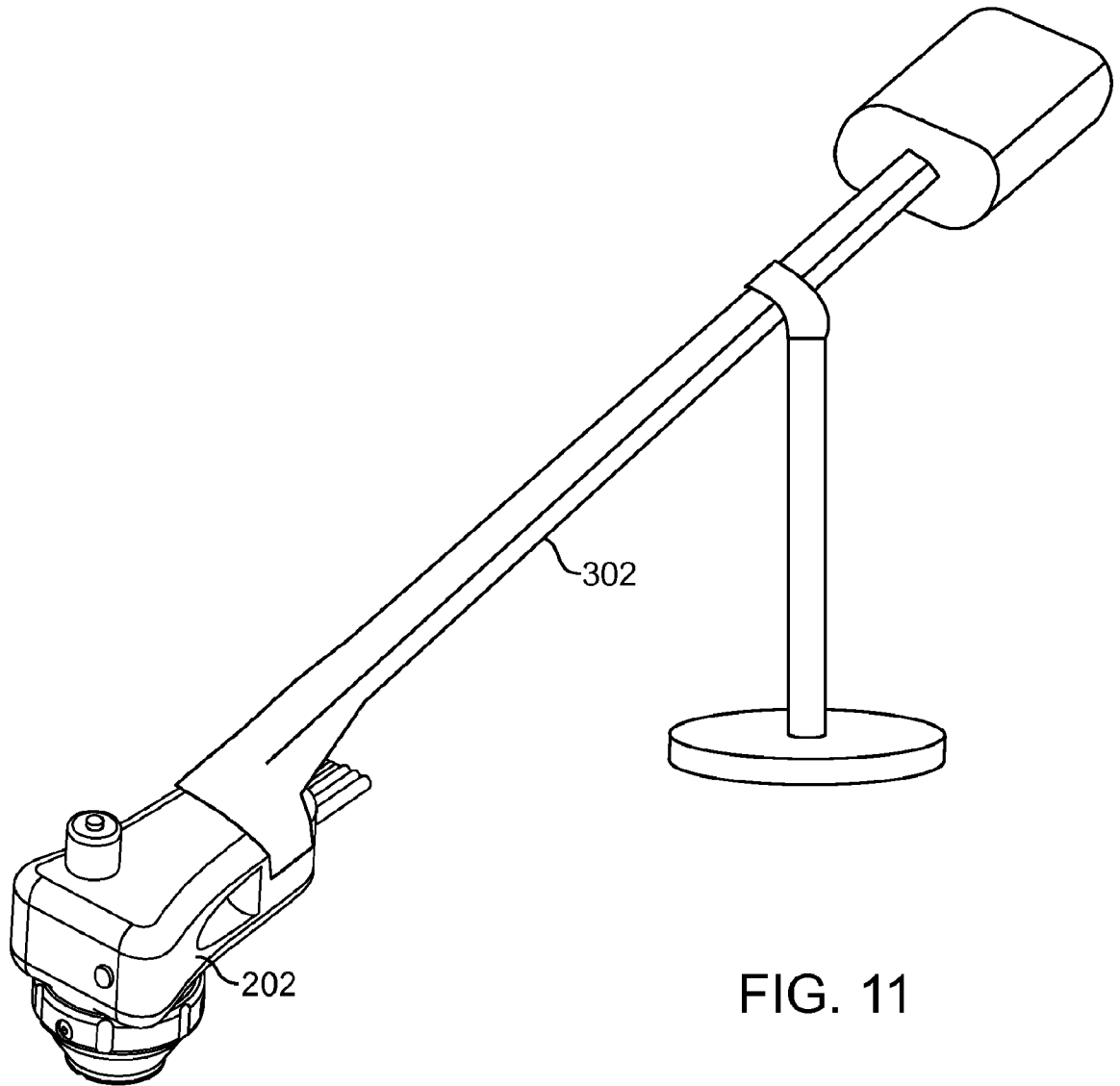


FIG. 10B



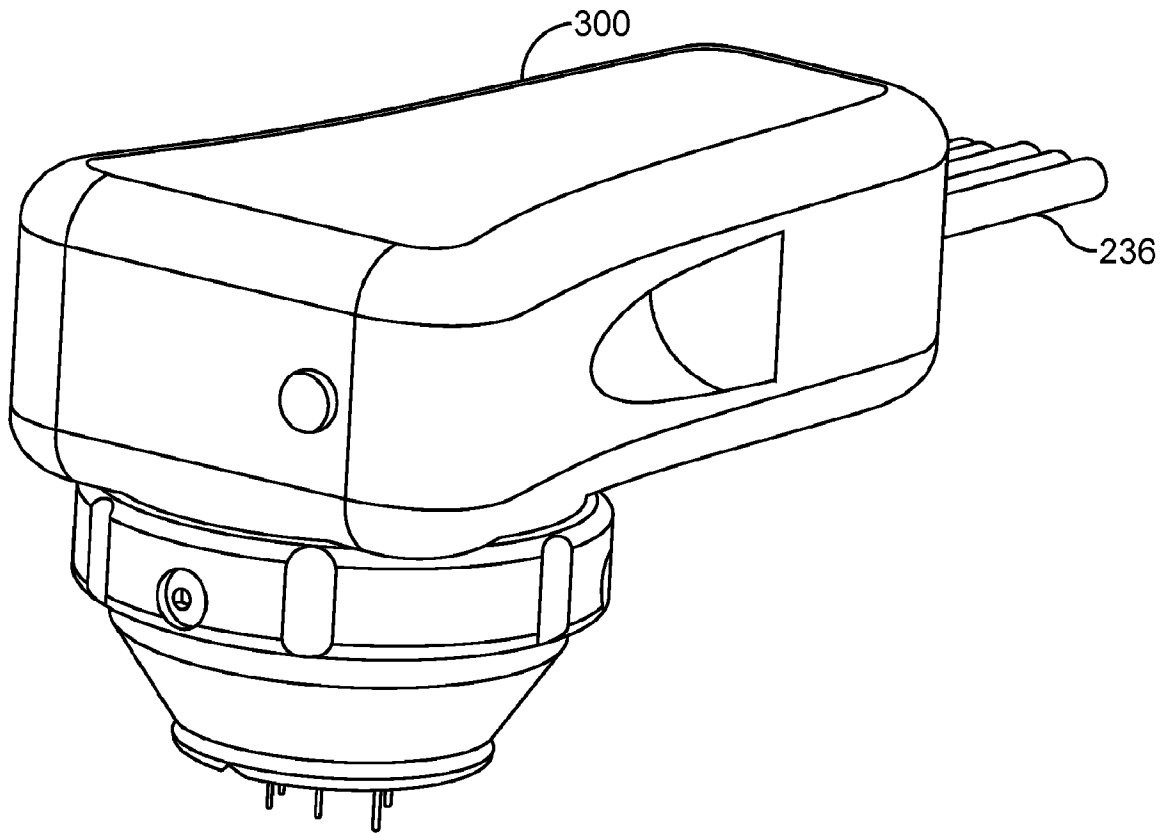


FIG. 12A

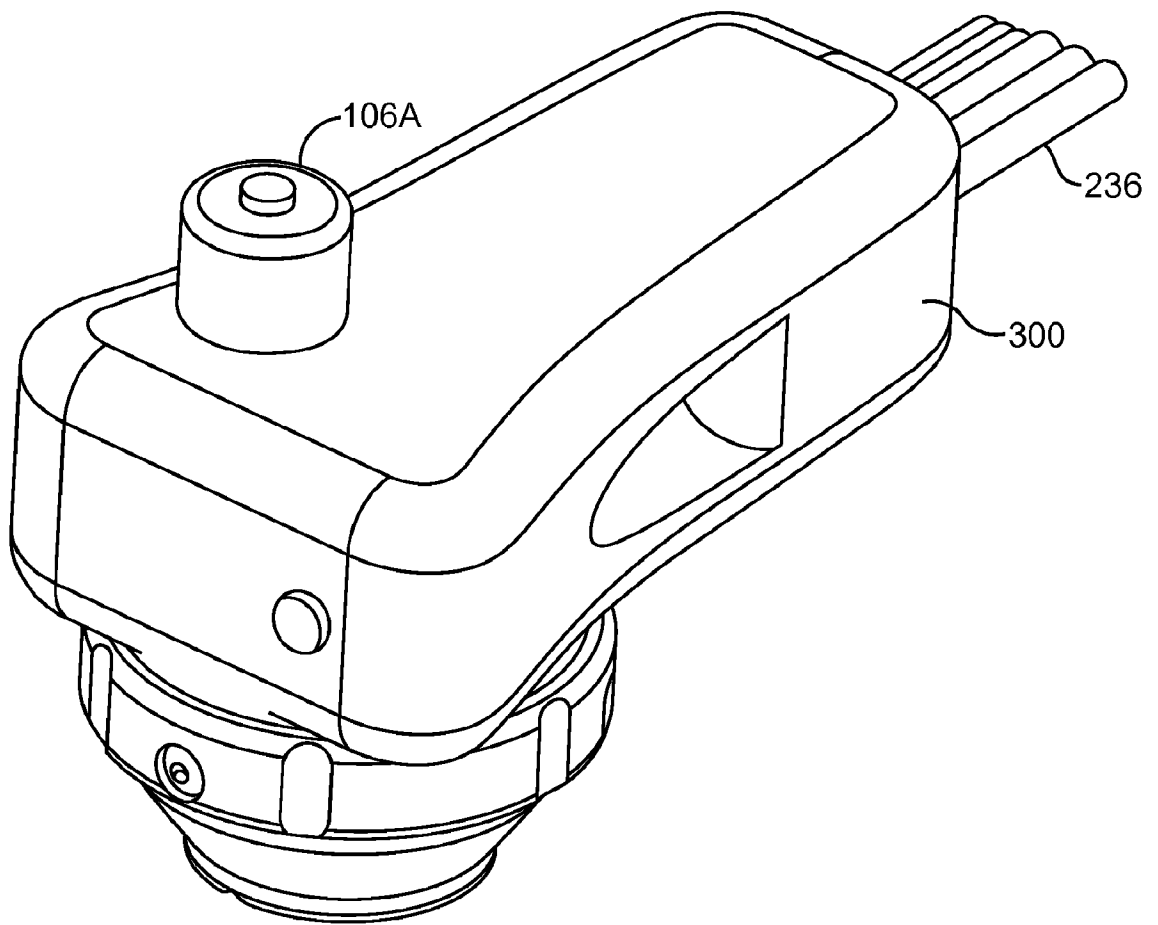


FIG. 12B

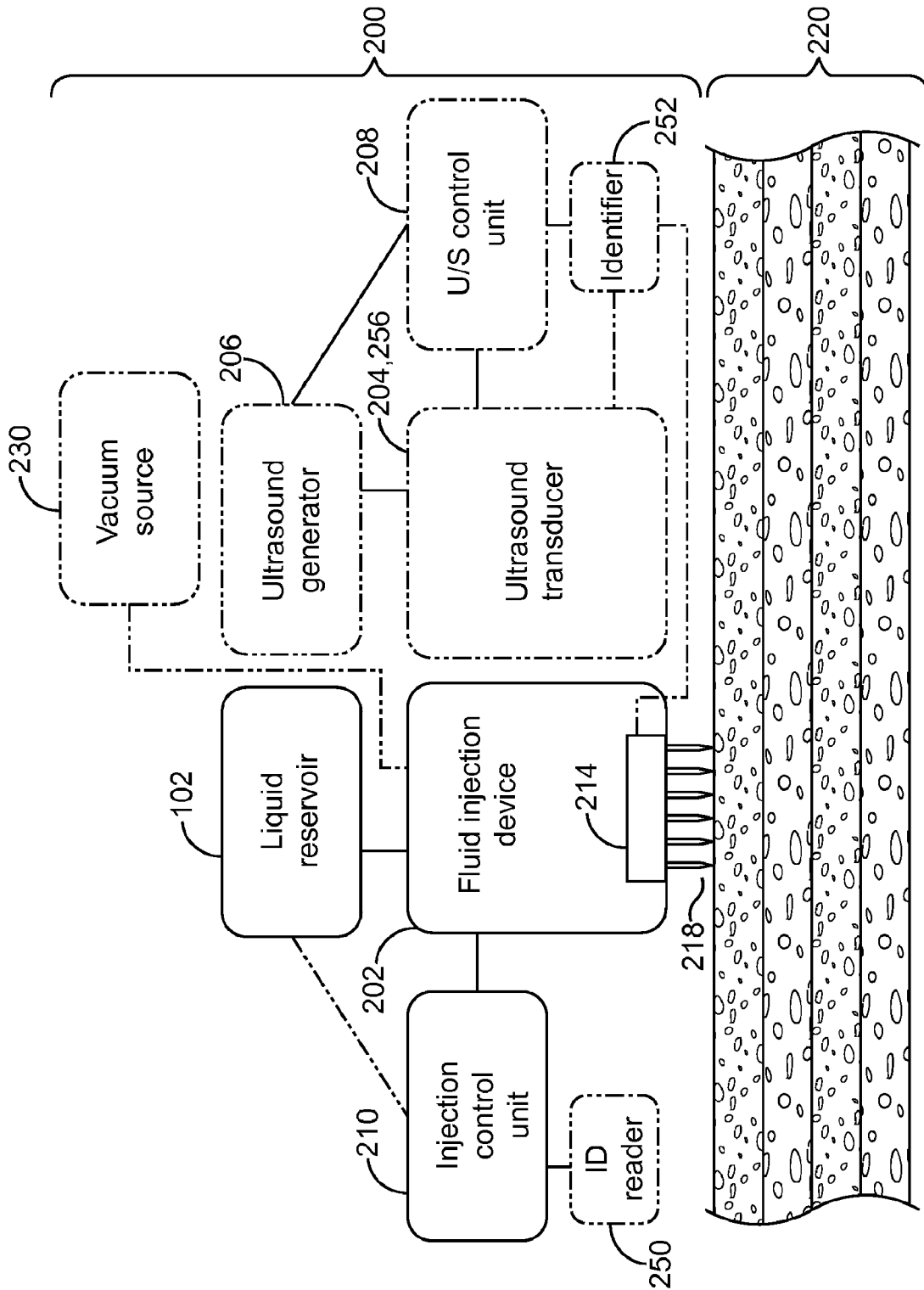


FIG. 13

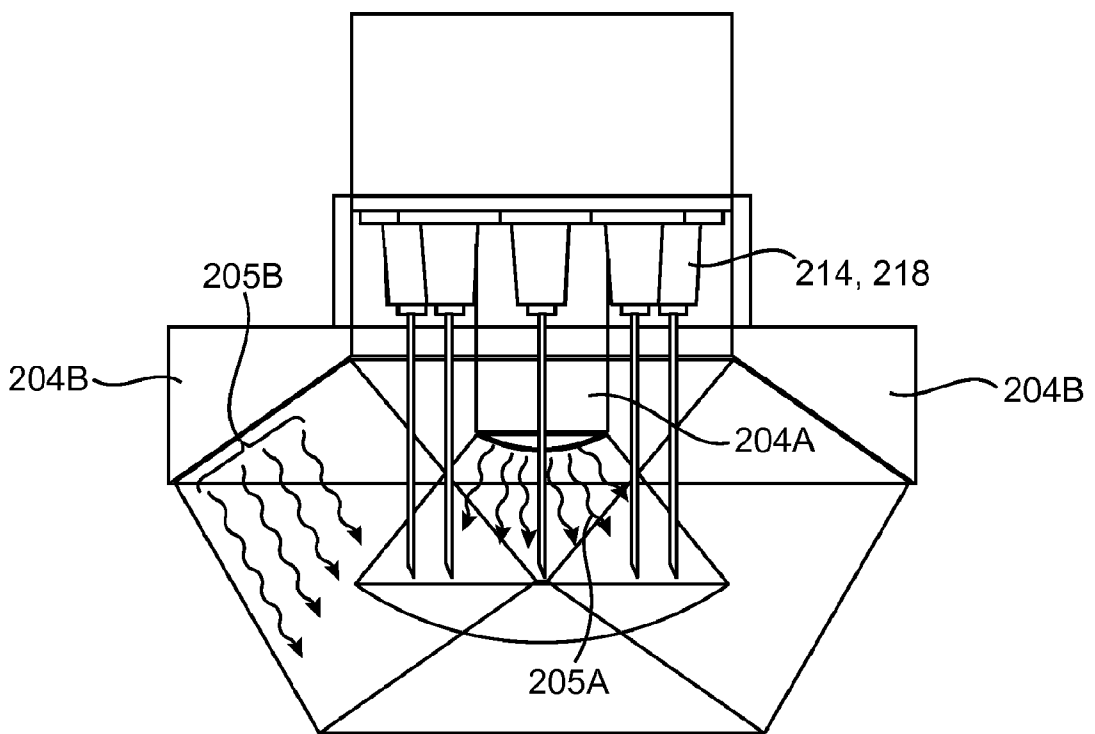


FIG. 14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/67124

<p>A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - C12N 13/00 (2008.04) USPC - 435/173.7 According to International Patent Classification (IPC) or to both national classification and IPC</p>																							
<p>B. FIELDS SEARCHED</p> <p>Minimum documentation searched (classification system followed by classification symbols) USPC: 435/173.7</p> <p>Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched USPC: All classes</p> <p>Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) PubWEST (PGPB, USPT, EPAB, JPAB), Google Scholar, Google Patents Keywords: Ultrasound, ultrasonic, sonic, lysing, transducer, wave, unfocused, nonfocused, defocused, microbubbles, vasoconstrictor, surfactant, anesthetic, epinephrine, oxygen, carbon, dioxide, perfluoropropane, argon, hydrogen, Halothane, Desflurane, Sevoflura</p>																							
<p>C. DOCUMENTS CONSIDERED TO BE RELEVANT</p> <table border="1" style="width:100%; border-collapse: collapse;"> <thead> <tr> <th style="width:10%;">Category*</th> <th style="width:70%;">Citation of document, with indication, where appropriate, of the relevant passages</th> <th style="width:20%;">Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td align="center">Y</td> <td>US 2004/0253183 A1 (UBER et al.) 16 December 2004 (16.12.2004) para [0009], [0026], [0060]-[0062], [0066], [0069], [0083], [0084], [0088], [0091]-[0094], [0132]</td> <td align="center">1-24, 27, 28</td> </tr> <tr> <td align="center">Y</td> <td>US 2002/0099356 A1 (UNGER et al.) 25 July 2002 (25.07.2002) para [0025], [0034], [0066], [0085], [0086]</td> <td align="center">1-23, 25-28</td> </tr> <tr> <td align="center">Y</td> <td>US 2004/0162546 A1 (LIANG et al.) 19 August 2004 (19.08.2004) para [0016]</td> <td align="center">7, 20-23, 25-28</td> </tr> <tr> <td align="center">Y</td> <td>US 2007/0043295 A1 (CHOMAS et al.) 22 September 2007 (22.09.2007) para [0008], [0022], [0040]</td> <td align="center">14-17</td> </tr> <tr> <td align="center">Y</td> <td>US 2003/0228254 A1 (KLAVENESS et al.) 11 December 2003 (11.12.2003) para [0356]</td> <td align="center">21-23</td> </tr> <tr> <td align="center">Y</td> <td>US 6,638,767 B2 (UNGER et al.) 28 October 2003 (28.10.2003) col 23, ln 16-24</td> <td align="center">24</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	Y	US 2004/0253183 A1 (UBER et al.) 16 December 2004 (16.12.2004) para [0009], [0026], [0060]-[0062], [0066], [0069], [0083], [0084], [0088], [0091]-[0094], [0132]	1-24, 27, 28	Y	US 2002/0099356 A1 (UNGER et al.) 25 July 2002 (25.07.2002) para [0025], [0034], [0066], [0085], [0086]	1-23, 25-28	Y	US 2004/0162546 A1 (LIANG et al.) 19 August 2004 (19.08.2004) para [0016]	7, 20-23, 25-28	Y	US 2007/0043295 A1 (CHOMAS et al.) 22 September 2007 (22.09.2007) para [0008], [0022], [0040]	14-17	Y	US 2003/0228254 A1 (KLAVENESS et al.) 11 December 2003 (11.12.2003) para [0356]	21-23	Y	US 6,638,767 B2 (UNGER et al.) 28 October 2003 (28.10.2003) col 23, ln 16-24	24
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<p><input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/></p>																							
<p>* Special categories of cited documents:</p> <table style="width:100%;"> <tr> <td style="width:50%;"> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </td> <td style="width:50%;"> <p>"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</p> <p>"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</p> <p>"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</p> <p>"&" document member of the same patent family</p> </td> </tr> </table>			<p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"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</p> <p>"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</p> <p>"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</p> <p>"&" document member of the same patent family</p>																			
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<p>Date of the actual completion of the international search 07 October 2008 (07.10.2008)</p>		<p>Date of mailing of the international search report 10 OCT 2008</p>																					
<p>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</p>		<p>Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774</p>																					