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solution comprises no more than 50 particles ≥10μm in diameter per ml. In one embodiment, the ophthalmic solution comprises no more than 2 particles ≥50μm in diameter per ml, no more than 5 particles ≥25μm in diameter per ml and no more than 50 particles ≥10μm in diameter per ml. In one embodiment, a syringe according to the invention meets USP789. In one embodiment the syringe has low levels of silicone oil sufficient for the syringe to meet USP789.

***VEGF Antagonists***

*Antibody VEGF antagonists*

VEGF is a well-characterised signal protein which stimulates angiogenesis. Two antibody VEGF antagonists have been approved for human use, namely ranibizumab (Lucentis®) and bevacizumab (Avastin®).

*Non-Antibody VEGF antagonists*

In one aspect of the invention, the non-antibody VEGF antagonist is an immunoadhesin. One such immuoadhesin is aflibercept (Eylea®), which has recently been approved for human use and is also known as VEGF-trap (Holash *et al.* (2002) *PNAS USA* 99:11393-98; Riely & Miller (2007) *Clin Cancer Res* 13:4623-7s). Aflibercept is the preferred non-antibody VEGF antagonist for use with the invention. Aflibercept is a recombinant human soluble VEGF receptor fusion protein consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1. It is a dimeric glycoprotein with a protein molecular weight of 97 kilodaltons (kDa) and contains glycosylation, constituting an additional 15% of the total molecular mass, resulting in a total molecular weight of 115 kDa. It is conveniently produced as a glycoprotein by expression in recombinant CHO K1 cells. Each monomer can have the following amino acid sequence (SEQ ID NO: 1):

SDTGRPFVEMYSEIPEIIHMTEGRELVIPCRVTSPNITVTLKKFPLDTLIPDGKRIIWDSRK
GFIISNATYKEIGLLTCEATVNGHLYKTNYLTHRQTNTIIDVVLSPSHGIELSVGEKLVLNC
TARTELNVGIDFNWEYPSSKHQHKKLVNRDLKTQSGSEMKKFLSTLTIDGVTRSDQGLY
TCAASSGLMTKKNSTFVRVHEKDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTP
EVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL
NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFY
PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE
ALHNHYTQKSLSLSPG

and disulfide bridges can be formed between residues 30-79, 124-185, 246-306 and 352-410 within each monomer, and between residues 211-211 and 214-214 between the monomers.

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Another non-antibody VEGF antagonist immunoadhesin currently in pre-clinical development is a recombinant human soluble VEGF receptor fusion protein similar to VEGF-trap containing extracellular ligand-binding domains 3 and 4 from VEGFR2/KDR, and domain 2 from VEGFR1/Flt-1; these domains are fused to a human IgG Fc protein fragment (Li et al., 2011 *Molecular Vision* 17:797-803). This antagonist binds to isoforms VEGF-A, VEGF-B and VEGF-C. The molecule is prepared using two different production processes resulting in different glycosylation patterns on the final proteins. The two glycoforms are referred to as KH902 (conbercept) and KH906. The fusion protein can have the following amino acid sequence (SEQ ID NO:2):

MVSYWDTGVLLCALLSCLLLTGSSSGGRPFVEMYSEIPEIIHMTEGRELVIPCRVTSPNIT
VTLKKFPLDTLIPDGKRIIWDSRKGFIISNATYKEIGLLTCEATVNGHLYKTNYLTHRQTNT
IIDVVLSPSHGIELSVGEKLVLNCTARTELNVGIDFNWEYPSSKHQHKKLVNRDLKTQSG
SEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHEKPFVAFGSGMESLVE
ATVGERVRLPAKYLGYPPPEIKWYKNGIPLESNHTIKAGHVLTIMEVSERDTGNYTVILTN
PISKEKQSHVVSLVVYVPPGPGDKTHTCPLCPAPELLGGPSVFLFPPKPKDTLMISRTPE
VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLN
GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP
SDIAVEWESNGQPENNYKATPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA
LHNHYTQKSLSLSPGK

and, like VEGF-trap, can be present as a dimer. This fusion protein and related molecules are further characterized in EP1767546.

Other non-antibody VEGF antagonists include antibody mimetics (*e.g.* Affibody® molecules, affilins, affitins, anticalins, avimers, Kunitz domain peptides, and monobodies) with VEGF antagonist activity. This includes recombinant binding proteins comprising an ankyrin repeat domain that binds VEGF-A and prevents it from binding to VEGFR-2. One example for such a molecule is DARPin® MP0112. The ankyrin binding domain may have the following amino acid sequence (SEQ ID NO: 3):

GSDLGKKLLEAARAGQDDEVRILMANGADVNTADSTGWTPLHLAVPWGHLEIVEVLLK
YGADVNAKDFQGWTPLHLAAAIGHQEIVEVLLKNGADVNAQDKFGKTAFDISIDNGNED
LAEILQKAA

Recombinant binding proteins comprising an ankyrin repeat domain that binds VEGF-A and prevents it from binding to VEGFR-2 are described in more detail in WO2010/060748 and WO2011/135067.

Further specific antibody mimetics with VEGF antagonist activity are the 40 kD pegylated anticalin PRS-050 and the monobody angiocept (CT-322).

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The afore-mentioned non-antibody VEGF antagonist may be modified to further improve their pharmacokinetic properties or bioavailability. For example, a non-antibody VEGF antagonist may be chemically modified (e.g., pegylated) to extend its *in vivo* half-life. Alternatively or in addition, it may be modified by glycosylation or the addition of further glycosylation sites not present in the protein sequence of the natural protein from which the VEGF antagonist was derived.

Variants of the above-specified VEGF antagonists that have improved characteristics for the desired application may be produced by the addition or deletion of amino acids. Ordinarily, these amino acid sequence variants will have an amino acid sequence having at least 60% amino acid sequence identity with the amino acid sequences of SEQ ID NO: 1, SEQ ID NO: 2 or SEQ ID NO: 3, preferably at least 80%, more preferably at least 85%, more preferably at least 90%, and most preferably at least 95%, including for example, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, and 100%. Identity or homology with respect to this sequence is defined herein as the percentage of amino acid residues in the candidate sequence that are identical with SEQ ID NO: 1, SEQ ID NO: 2 or SEQ ID NO: 3, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity.

Sequence identity can be determined by standard methods that are commonly used to compare the similarity in position of the amino acids of two polypeptides. Using a computer program such as BLAST or FASTA, two polypeptides are aligned for optimal matching of their respective amino acids (either along the full length of one or both sequences or along a pre-determined portion of one or both sequences). The programs provide a default opening penalty and a default gap penalty, and a scoring matrix such as PAM 250 [a standard scoring matrix; see Dayhoff et al., in Atlas of Protein Sequence and Structure, vol. 5, supp. 3 (1978)] can be used in conjunction with the computer program. For example, the percent identity can then be calculated as: the total number of identical matches multiplied by 100 and then divided by the sum of the length of the longer sequence within the matched span and the number of gaps introduced into the longer sequences in order to align the two sequences.

Preferably, the non-antibody VEGF antagonist of the invention binds to VEGF via one or more protein domain(s) that are not derived from the antigen-binding domain of an antibody. The non-antibody VEGF antagonist of the invention are preferably proteinaceous, but may include modifications that are non-proteinaceous (e.g., pegylation, glycosylation).

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***Therapy***

The syringe of the invention may be used to treat an ocular disease, including but not limited to choroidal neovascularisation, age-related macular degeneration (both wet and dry forms), macular edema secondary to retinal vein occlusion (RVO) including both branch RVO (bRVO) and central RVO (cRVO), choroidal neovascularisation secondary to pathologic myopia (PM), diabetic macular edema (DME), diabetic retinopathy, and proliferative retinopathy.

Thus the invention provides a method of treating a patient suffering from of an ocular disease selected from choroidal neovascularisation, wet age-related macular degeneration, macular edema secondary to retinal vein occlusion (RVO) including both branch RVO (bRVO) and central RVO (cRVO), choroidal neovascularisation secondary to pathologic myopia (PM), diabetic macular edema (DME), diabetic retinopathy, and proliferative retinopathy, comprising the step of administering an ophthalmic solution to the patient using a pre-filled syringe of the invention. This method preferably further comprises an initial priming step in which the physician depresses the plunger of the pre-filled syringe to align the pre-determined part of the stopper with the priming mark.

In one embodiment, the invention provides a method of treating an ocular disease selected from choroidal neovascularisation, wet age-related macular degeneration, macular edema secondary to retinal vein occlusion (RVO) including both branch RVO (bRVO) and central RVO (cRVO), choroidal neovascularisation secondary to pathologic myopia (PM), diabetic macular edema (DME), diabetic retinopathy, and proliferative retinopathy, comprising administering a non-antibody VEGF antagonist with a pre-filled syringe of the invention, wherein the patient has previously received treatment with an antibody VEGF antagonist.

***Kits***

Also provided are kits comprising the pre-filled syringes of the invention. In one embodiment, such a kit comprises a pre-filled syringe of the invention in a blister pack. The blister pack may itself be sterile on the inside. In one embodiment, syringes according to the invention may be placed inside such blister packs prior to undergoing sterilisation, for example terminal sterilisation.

Such a kit may further comprise a needle for administration of the VEGF antagonist. If the VEGF antagonist is to be administered intravitreally, it is typical to use a 30-gauge x ½ inch needle, though 31-gauge and 32-gauge needles may be used. For intravitreal administration, 33-gauge or 34-gauge needles could alternatively be used. Such kits may further comprise instructions for use. In one embodiment, the invention provides a carton

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containing a pre-filled syringe according to the invention contained within a blister pack, a needle and optionally instructions for administration.

***Sterilisation***

As noted above, a terminal sterilisation process may be used to sterilise the syringe and such a process may use a known process such as an ethylene oxide or a hydrogen peroxide sterilisation process. Needles to be used with the syringe may be sterilised by the same method, as may kits according to the invention.

The package is exposed to the sterilising gas until the outside of the syringe is sterile. Following such a process, the outer surface of the syringe may remain sterile (whilst in its blister pack) for up to 6 months, 9 months, 12 months, 15 months, 18 months or longer. In one embodiment, less than one syringe in a million has detectable microbial presence on the outside of the syringe after 18 months of storage. In one embodiment, the pre-filled syringe has been sterilised using EtO with a Sterility Assurance Level of at least $10^{-6}$. In one embodiment, the pre-filled syringe has been sterilised using hydrogen peroxide with a Sterility Assurance Level of at least $10^{-6}$. Of course, it is a requirement that significant amounts of the sterilising gas should not enter the variable volume chamber of the syringe. The term "significant amounts" as used herein refers to an amount of gas that would cause unacceptable modification of the ophthalmic solution within the variable volume chamber. In one embodiment, the sterilisation process causes $\leq$10% (preferably $\leq$5%, $\leq$3%, $\leq$1%) alkylation of the VEGF antagonist. In one embodiment, the pre-filled syringe has been sterilised using EtO, but the outer surface of the syringe has $\leq$1ppm, preferably $\leq$0.2ppm EtO residue. In one embodiment, the pre-filled syringe has been sterilised using hydrogen peroxide, but the outer surface of the syringe has $\leq$1ppm, preferably $\leq$0.2ppm hydrogen peroxide residue. In another embodiment, the pre-filled syringe has been sterilised using EtO, and the total EtO residue found on the outside of the syringe and inside of the blister pack is $\leq$0.1mg. In another embodiment, the pre-filled syringe has been sterilised using hydrogen peroxide, and the total hydrogen peroxide residue found on the outside of the syringe and inside of the blister pack is $\leq$0.1mg.

***General***

The term "comprising" means "including" as well as "consisting" *e.g.* a composition "comprising" X may consist exclusively of X or may include something additional *e.g.* X + Y.

The term "about" in relation to a numerical value *x* means, for example, $x\pm$10%.

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References to a percentage sequence identity between two amino acid sequences means that, when aligned, that percentage of amino acids are the same in comparing the two sequences. This alignment and the percent homology or sequence identity can be determined using software programs known in the art, for example those described in section 7.7.18 of *Current Protocols in Molecular Biology* (F.M. Ausubel *et al.*, eds., 1987) Supplement 30. A preferred alignment is determined by the Smith-Waterman homology search algorithm using an affine gap search with a gap open penalty of 12 and a gap extension penalty of 2, BLOSUM matrix of 62. The Smith-Waterman homology search algorithm is disclosed in Smith & Waterman (1981) *Adv. Appl. Math.* 2: 482-489

**BRIEF DESCRIPTION OF THE FIGURES**

Figure 1 shows a side view of a syringe

Figure 2 shows a cross section of a top down view of a syringe

Figure 3 shows a view of a plunger

Figure 4 shows a cross section though a plunger

Figure 5 shows a stopper

**MODES FOR CARRYING OUT THE INVENTION**

The invention will now be further described, by way of example only, with reference to the drawings.

Figure 1 shows a view from a side of a syringe 1 comprising a body 2, plunger 4, backstop 6 and a sealing device 8.

Figure 2 shows a cross section through the syringe 1 of Figure 1 from above. The syringe 1 is suitable for use in an ophthalmic injection. The syringe 1 comprises a body 2, a stopper 10 and a plunger 4. The syringe 1 extends along a first axis A. The body 2 comprises an outlet 12 at an outlet end 14 and the stopper 10 is arranged within the body 2 such that a front surface 16 of the stopper 10 and the body 2 define a variable volume chamber 18. The variable volume chamber 18 contains an injectable medicament 20 comprising an ophthalmic solution comprising a VEGF antagonist such as ranibizumab. The injectable fluid 20 can be expelled though the outlet 12 by movement of the stopper 10 towards the outlet end 14 thereby reducing the volume of the variable volume chamber 18. The plunger 4 comprises a plunger contact surface 22 at a first end 24 and a rod 26 extending between the plunger contact surface 22 and a rear portion 25. The plunger contact surface 22 is arranged to contact the stopper 10, such that the plunger 4 can be used to move the stopper 10 towards the outlet end 14 of

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the body 2. Such movement reduces the volume of the variable volume chamber 18 and causes fluid therein to be expelled though the outlet.

The backstop 6 is attached to the body 2 by coupling to a terminal flange 28 of the body 2. The backstop 6 includes sandwich portion 30 which is adapted to substantially sandwich at least some of the terminal flange 28 of the body 2. The backstop 6 is adapted to be coupled to the body 2 from the side by leaving one side of the backstop 6 open so that the backstop 6 can be fitted to the syringe 2.

The body 2 defines a substantially cylindrical bore 36 which has a bore radius. The rod 26 comprises a rod shoulder 32 directed away from the outlet end 14. The rod shoulder 32 extends from to a rod shoulder radius from the first axis A which is such that it is slightly less than the bore radius so that the shoulder fits within the bore 36. The backstop 6 includes a backstop shoulder 34 directed towards the outlet end 14. The shoulders 32, 34 are configured to cooperate to substantially prevent movement of the rod 26 away from the outlet end 14 when the backstop shoulder 34 and rod shoulder 32 are in contact. The backstop shoulder 34 extends from outside the bore radius to a radius less than the rod shoulder radius so that the rod shoulder 32 cannot pass the backstop shoulder 34 by moving along the first axis A. In this case the rod shoulder 32 is substantially disc, or ring, shaped and the backstop shoulder 34 includes an arc around a rear end 38 of the body 2.

The backstop 6 also includes two finger projections 40 which extend in opposite directions away from the body 2 substantially perpendicular to the first axis A to facilitate manual handling of the syringe 1 during use.

In this example the syringe comprises a 0.5ml body 2 filled with between about 0.1 and 0.3 ml of an injectable medicament 20 comprising a 10mg/ml injectable solution comprising ranibizumab. The syringe body 2 has an internal diameter of about between about 4.5mm and 4.8mm, a length of between about 45mm and 50mm.

The plunger 4 and stopper 10 will be described in more detail with reference to later figures.

Figure 3 shows a perspective view of the plunger 4 of Figure 1 showing the plunger contact surface 22 at the first end 24 of the plunger 4. The rod 26 extends from the first end 24 to the rear portion 25. The rear portion 25 includes a disc shaped flange 42 to facilitate user handling of the device. The flange 42 provides a larger surface area for contact by the user than a bare end of the rod 26.

Figure 4 shows a cross section though a syringe body 2 and rod 26. The rod 26 includes four longitudinal ribs 44 and the angle between the ribs is 90°.

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Figure 5 shows a detailed view of a stopper 10 showing a conical shaped front surface 16 and three circumferential ribs 52,54,56 around a substantially cylindrical body 58. The axial gap between the first rib 52 and the last rib 56 is about 3mm. The rear surface 60 of the stopper 10 includes a substantially central recess 62. The central recess 62 includes an initial bore 64 having a first diameter. The initial bore 64 leading from the rear surface 60 into the stopper 10 to an inner recess 66 having a second diameter, the second diameter being larger than the first diameter.

***Stopper forces***

0.5ml syringes siliconised with <100µg silicone oil, filled with Lucentis, comprising one of two different stopper designs were tested for maximal and average break out and slide force. Prior to testing, 30G x 0.5" needles were attached to the syringes. The testing was carried out at a stopper speed of 190mm/min over a travel length of 10.9mm.

| | | Stopper design 1 | | | Stopper design 2 | |
|---|---|---|---|---|---|---|
| | | Batch A | Batch B | Batch C | Batch D | Batch E |
| Break loose force of syringes | Average of 10 syringes | 2.2N | 2.3N | 1.9N | 2.1N | 2.5N |
| | Max individual value | 2.5N | 2.5N | 2.3N | 2.6N | 2.7N |
| Sliding force | Average of 10 syringes | 3.1N | 3.2N | 3.1N | 4.1N | 4.6N |
| | Max individual value | 3.5N | 3.5N | 3.6N | 4.7N | 4.8N |

For both stopper designs, average and maximum break out force remained below 3N. For both stopper designs, average and maximum sliding force remained below 5N.

It will be understood that the invention has been described by way of example only and modifications may be made whilst remaining within the scope and spirit of the invention.

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**Claims**

1. A pre-filled syringe, the syringe comprising a body, a stopper and a plunger, the body comprising an outlet at an outlet end and the stopper being arranged within the body such that a front surface of the stopper and the body define a variable volume chamber from which a fluid can be expelled though the outlet, the plunger comprising a plunger contact surface at a first end and a rod extending between the plunger contact surface and a rear portion, the plunger contact surface arranged to contact the stopper, such that the plunger can be used to force the stopper towards the outlet end of the body, reducing the volume of the variable volume chamber, characterised in that the fluid is an ophthalmic solution which comprises a VEGF-antagonist, wherein

   (a) the syringe has a nominal maximum fill volume of between about 0.5ml and about 1ml,

   (b) the syringe is filled with between about 0.15ml and about 0.175ml of said VEGF antagonist solution which comprises a dosage volume of about 0.05ml of said VEGF antagonist solution,

   (c) the syringe barrel comprises less than about 500µg silicone oil,

   (d) the VEGF antagonist solution comprises no more than 2 particles ≥50µm in diameter per ml, and

   (e) the VEGF antagonist is the antibody VEGF antagonist bevacizumab.

2. A pre-filled syringe, the syringe comprising a body, a stopper and a plunger, the body comprising an outlet at an outlet end and the stopper being arranged within the body such that a front surface of the stopper and the body define a variable volume chamber from which a fluid can be expelled though the outlet, the plunger comprising a plunger contact surface at a first end and a rod extending between the plunger contact surface and a rear portion, the plunger contact surface arranged to contact the stopper, such that the plunger can be used to force the stopper towards the outlet end of the body, reducing the volume of the variable volume chamber, characterised in that the fluid is an ophthalmic solution which comprises a VEGF-antagonist, wherein

   (a) the syringe has a nominal maximum fill volume of between about 0.5ml and about 1ml,

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(b) the syringe is filled with between about 0.15ml and about 0.175ml of said VEGF antagonist solution which comprises a dosage volume of about 0.05ml of said VEGF antagonist solution,

(c) the syringe barrel comprises less than about 500µg silicone oil,

(d) the VEGF antagonist solution comprises no more than 2 particles ≥50µm in diameter per ml, and

(e) the VEGF antagonist is the antibody VEGF antagonist bevacizumab at a concentration of 25 mg/ml.

3. A pre-filled syringe according to claim 1 or 2, wherein the syringe is filled with about 0.165ml of said VEGF antagonist solution.

4. A pre-filled syringe according to any previous claim, wherein the syringe barrel has an internal coating of silicone oil that has an average thickness of about 450nm or less.

5. A pre-filled syringe according to any previous claim, wherein the syringe barrel has an internal coating of less than about 500 µg silicone oil, preferably less than about 100µg silicone oil, preferably less than about 50µg silicone oil, preferably less than about 25µg silicone oil.

6. A pre-filled syringe according to any previous claim, wherein the silicone oil is DC365 emulsion.

7. A pre-filled syringe according to any previous claim, wherein the syringe is silicone oil free.

8. A pre-filled syringe according to any previous claim, wherein the VEGF antagonist solution further comprises one or more of (i) no more than 5 particles ≥25µm in diameter per ml, and (ii) no more than 50 particles ≥10µm in diameter per ml.

9. A pre-filled syringe according to any previous claim, wherein the VEGF antagonist solution meets USP789.

10. A pre-filled syringe according to any previous claim, wherein the syringe has a stopper break loose force of less than about 11N.

11. A pre-filled syringe according to claim 10, wherein the syringe has a stopper break loose force of less than about 5N.

12. A pre-filled syringe according to any previous claim, wherein the syringe has a stopper slide force of less than about 11N.

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13. A pre-filled syringe according to claim 12, wherein the syringe has a stopper slide force of less than about 5N.

14. A pre-filled syringe according to any previous claim, in which the dosage volume is determined by volume of the variable volume chamber when a predetermined part of the stopper or plunger is aligned with a priming mark on the syringe

15. A blister pack comprising a pre-filled syringe according to any previous claim, wherein the syringe has been sterilised using $H_2O_2$ or EtO.

16. A blister pack comprising a pre-filled syringe according to claim 15, wherein the outer surface of the syringe has $\leq$1ppm EtO or $H_2O_2$ residue.

17. A blister pack comprising a pre-filled syringe according to claim 15, wherein the syringe has been sterilised using EtO or $H_2O_2$ and the total EtO or $H_2O_2$ residue found on the outside of the syringe and inside of the blister pack is $\leq$0.1mg.

18. A blister pack comprising a pre-filled syringe according to any one of claims 15-17, wherein $\leq$5% of the VEGF antagonist is alkylated.

19. A blister pack comprising a pre-filled syringe according to any of claims 15-18, wherein the syringe has been sterilised using EtO or hydrogen peroxide with a Sterility Assurance Level of at least $10^{-6}$.

20. A kit comprising: (i) a pre-filled syringe according to any one of claims 1-14, or a blister pack comprising a pre-filled syringe according to any one of claims 15-19, (ii) a needle, and optionally (iii) instructions for administration.

21. A kit according to claim 20, wherein the needle is a 30-gauge x ½ inch needle.

22. A pre-filled syringe according to any one of claims 1-14 for use in therapy.

23. A pre-filled syringe according to any one of claims 1-14 for use in the treatment of an ocular disease selected from choroidal neovascularisation, wet age-related macular degeneration, macular edema secondary to retinal vein occlusion (RVO) including both branch RVO (bRVO) and central RVO (cRVO), choroidal neovascularisation secondary to pathologic myopia (PM), diabetic macular edema (DME), diabetic retinopathy, and proliferative retinopathy.

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1/1

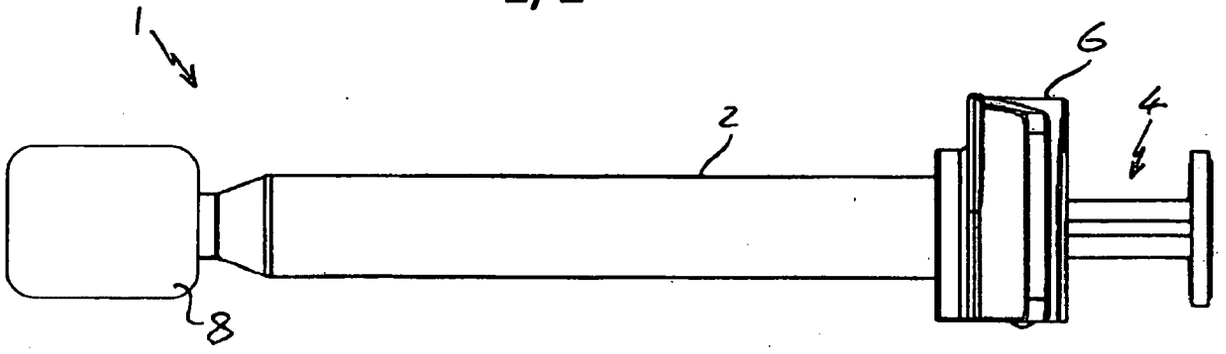


Fig 1

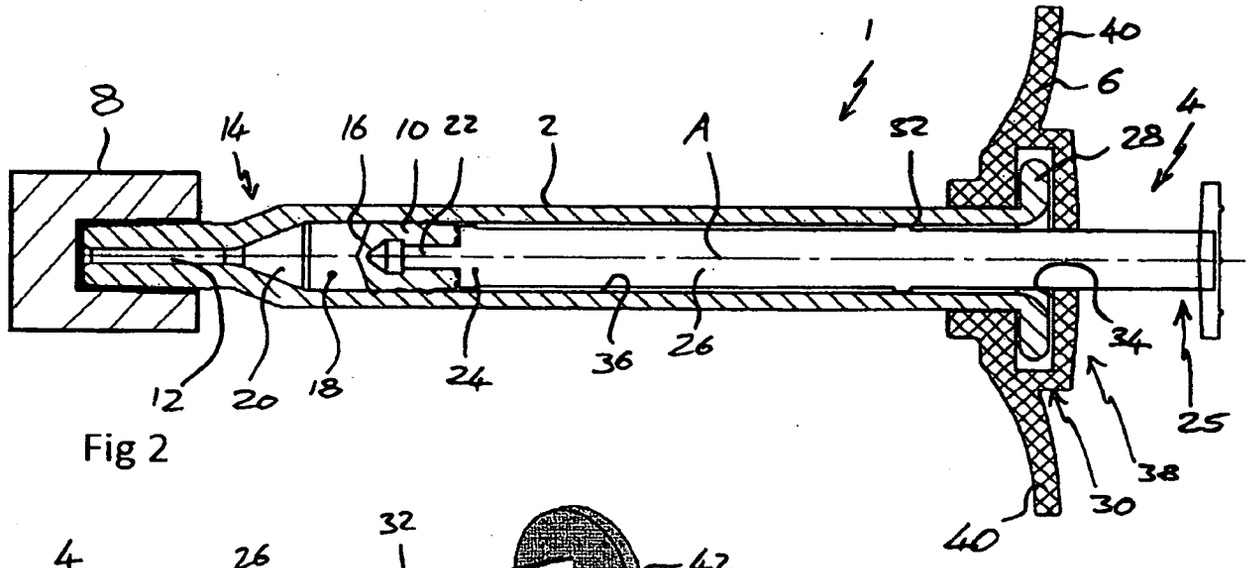


Fig 2

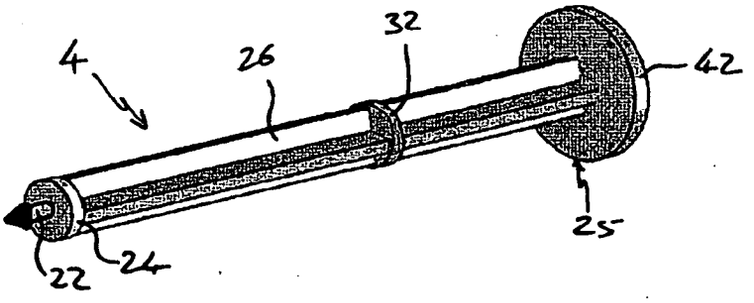


Fig 3

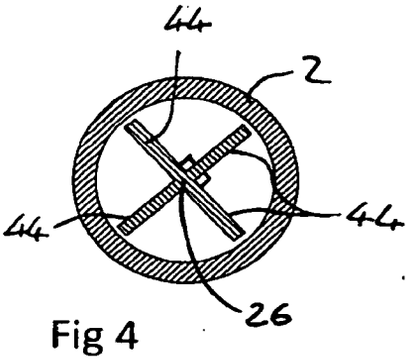


Fig 4

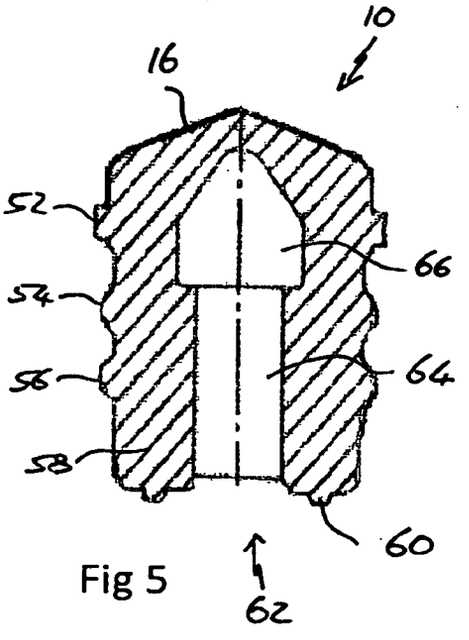


Fig 5

DocCode – SCORE

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# BUNDESREPUBLIK DEUTSCHLAND

## Prioritätsbescheinigung
## DE 20 2013 000 688.9
## über die Einreichung einer Gebrauchsmusteranmeldung

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| **IPC:** | A61F 9/00; A61M 5/178 |

**Die angehefteten Stücke sind eine richtige und genaue Wiedergabe der Teile der am 23. Januar 2013 eingereichten Unterlagen dieser Gebrauchsmusteranmeldung unabhängig von gegebenenfalls durch das Kopierverfahren bedingten Farbabweichungen.**

München, den 28. Februar 2013
**Deutsches Patent- und Markenamt**
**Die Präsidentin**
Im Auftrag

Schäfer

23_01_2013-01-00003-00000106



**Beschreibung**

**GLAS-SPRITZE**

**TECHNISCHES GEBIET**

Die vorliegende Erfindung betrifft eine Spritze, insbesondere eine kleinvolumige Spritze, die sich zum Verabreichen ophthalmischer Injektionen eignet.

**STAND DER TECHNIK**

Patienten werden viele Medikamente mit Hilfe einer Spritze verabreicht, mit der der Anwender das Medikament anwenden kann. Wird einem Patienten ein Medikament in einer Spritze verabreicht, geschieht dies oft, um es dem Patienten oder einer Pflegeperson zu ermöglichen, das Medikament selbst zu injizieren. Für die Patientensicherheit und die Unversehrtheit des Medikaments ist es wichtig, dass die Spritze und deren Inhalte ausreichend steril sind, um Infektionen und andere Risiken für die Patienten zu vermeiden. Die Sterilisation kann durch eine abschließende Sterilisation erreicht werden, bei der das zusammengefügte Produkt, das sich typischerweise bereits in der dazugehörigen Verpackung befindet, unter Zuhilfenahme von Hitze oder eines sterilisierenden Gases sterilisiert wird.

Im Fall von kleinvolumigen Spritzen, zum Beispiel jenen für Injektionen in das Auge, bei denen beabsichtigt ist, dass ungefähr 0,1 ml oder weniger der Flüssigkeit injiziert werden sollen, kann die Sterilisation zu Problemen führen, die bei größeren Spritzen nicht unbedingt auftreten. Druckveränderungen innerhalb oder außerhalb der Spritze können dazu führen, dass sich Teile der Spritze unvorhersehbar bewegen, was Dichteeigenschaften verändern und unter Umständen die Sterilität beeinträchtigen kann.

Zudem sind bestimmte Therapeutika, wie biologische Moleküle, besonders sterilisationsempfindlich, handelt es sich um eine kalte Gassterilisation, eine thermische Sterilisation oder eine Bestrahlung. Daher ist ein vorsichtiger Balanceakt notwendig, um sicherstellen, dass, während ein geeigneter Sterilisationsgrad erreicht wird, die Spritze weiterhin entsprechend abgedichtet bleibt, damit das Therapeutikum nicht beeinträchtigt wird. Selbstverständlich muss die Spritze leicht handhabbar bleiben, insofern dass die Kraft, die erforderlich ist, um den Kolben herabzudrücken, um das Medikament zu verabreichen, nicht zu hoch sein darf.

Deshalb besteht ein Bedarf nach einer neuen Spritzenkonstruktion, die eine stabile Abdichtung für ihre Inhalte bietet, aber eine leichte Handhabung beibehält.

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**OFFENBARUNG DER ERFINDUNG**

Die vorliegende Erfindung stellt eine vorgefüllte Spritze bereit, die Spritze umfasst einen Körper, einen Stopper und einem Kolben, wobei der Körper an einem Auslass-Ende einen Auslass umfasst und der Stopper im Körper so angeordnet ist, dass die frontale Oberfläche des Stoppers und der Körper eine Kammer mit variablem Volumen bzw. variable Volumenkammer beschreiben, aus der eine Flüssigkeit durch den Auslass gedrückt wird, der Kolben umfasst eine Kolbenkontaktfläche an einem ersten Ende und einen Stab, der sich zwischen der Kolbenkontaktfläche und einem hinteren Anteil erstreckt, die Kolbenkontaktfläche ist derart angeordnet, um den Stopper zu berühren, damit der Kolben dazu benutzt werden kann, den Stopper zum Auslass-Ende des Körpers zu drücken, wobei das Volumen der Kammer mit variablem Volumen vermindert wird, gekennzeichnet dadurch, dass die Flüssigkeit eine ophthalmische Lösung umfasst. In einer Ausführungsform umfasst die ophthalmische Lösung einen VEGF-Antagonisten.

In einer Ausführungsform eignet sich die Spritze für ophthalmische Injektionen, insbesondere intravitreale Injektionen und verfügt daher über ein geeignet geringes Volumen. Die Spritze kann auch frei von Silikonöl sein oder nahezu frei von Silikonöl sein, oder kann eine geringe Menge an Silikonöl als Schmiermittel enthalten. Gemäß einer Ausführungsform beträgt die Losbrechkraft und Gleitkraft des Stoppers trotz der geringen Menge an Silikonöl weniger als 20 N.

Bei ophthalmischen Injektionen ist es für die ophthalmische Lösung von erheblicher Bedeutung einen besonders niedrigen Partikelgehalt aufzuweisen. In einer Ausführungsform entspricht die Spritze der Anforderung des Standards 789 (USP 789) des US Arzneimittelbuchs (engl.: *US Pharmacopeia*).

**Spritze**

Der Körper der Spritze kann im Wesentlichen eine zylindrische Hülle sein oder kann im Wesentlichen eine zylindrische Bohrung mit einer nicht kreisförmigen äußeren Form einschließen. Das Auslass-Ende des Körpers schließt einen Auslass ein, durch den eine Flüssigkeit, die sich innerhalb der variablen Volumenkammer befindet, herausgedrückt werden kann, während das Volumen der besagten Kammer vermindert wird. Der Auslass kann einen Vorsprung vom Auslass-Ende umfassen, durch den sich ein Kanal erstreckt mit einem kleineren Durchmesser als der Durchmesser der variablen Volumenkammer. Der Auslass kann, zum Beispiel über eine Luer-Lock-Verbindung, für die Verbindung mit einer Nadel oder anderem Zubehör, wie einer Dichtungsvorrichtung, die die variable Volumenkammer abdichten kann, gestaltet sein, er kann aber genutzt oder entfernt werden, um die variable Volumenkammer zu entsiegeln und erlaubt eine

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Verbindung der Spritze mit anderem Zubehör, wie zum Beispiel einer Nadel. Eine solche Verbindung kann direkt zwischen der Spritze und dem Zubehör oder unter Zuhilfenahme der Dichtungsvorrichtung hergestellt werden. Der Körper erstreckt sich entlang einer ersten Achse vom Auslass-Ende zum hinteren Ende.

Der Körper kann aus Kunststoff (z.B. ein zyklisches Olefinpolymer) oder Glas hergestellt werden und kann Spuren davon auf einer Oberfläche einschließen, um als Injektionsführung zu wirken. In einer Ausführungsform kann der Spritzenkörper über eine Füllmarkierung verfügen. Diese ermöglicht es dem Behandelnden, einen zuvor festgelegten Teil des Stoppers (wie die Spitze der vorderen Oberfläche oder eine der umlaufenden Lamellen, wie später besprochen) oder Kolbens an der Markierung auszurichten, wodurch überschüssige ophthalmische Lösung oder jegliche Luftblasen aus der Spritze gedrückt werden. Der Füllvorgang stellt sicher, dass dem Patienten eine genaue zuvor festgelegte Dosis verabreicht wird.

Der Stopper kann aus Gummi, Silikon oder aus einem anderen geeigneten elastisch verformbaren Material hergestellt sein. Im Wesentlichen kann der Stopper eine zylindrische Form aufweisen, und der Stopper kann eine oder mehrere umlaufende Lamellen um eine äußere Oberfläche des Stoppers einschließen, der Stopper und die Lamellen sind dabei so ausgelegt, dass die Lamellen mit einer inneren Oberfläche des Spritzenkörpers für eine im Wesentlichen flüssigkeitsbeständige Abdichtung sorgen. Die frontale Oberfläche des Stoppers kann irgendeine geeignete Form aufweisen, zum Beispiel im Wesentlichen eben, im Wesentlichen konisch oder gewölbt. Die hintere Oberfläche des Stoppers kann über eine zentrale Aussparung verfügen. Eine solche Aussparung könnte genutzt werden, um einen Kolben mit dem Stopper zu verbinden, unter Verwendung einer Schnappvorrichtung oder eines Gewindeanschluss auf bekannte Weise. Der Stopper kann im Wesentlichen rotationssymmetrisch zu einer Achse durch den Stopper vorliegen.

Der Kolben umfasst eine Kolbenkontaktfläche, und ausgehend davon erstreckt sich ein Stab von der Kolbenkontaktfläche bis zum einem hinteren Anteil. Der hintere Anteil kann über ein Kontaktteil für einen Benutzer verfügen, der so gestaltet ist, dass er von einem Benutzer bei einer Injektion berührt wird. Das Kontaktteil für einen Benutzer kann einen im Wesentlichen scheibenförmigen Teil umfassen, der Radius der Scheibe erstreckt sich im Wesentlichen senkrecht zur der Achse, entlang welcher der Stab verläuft. Das Kontaktteil für einen Benutzer könnte jede geeignete Form aufweisen. Die Achse, entlang welcher der Stab verläuft, kann die erste Achse sein oder kann im Wesentlichen parallel zur ersten Achse verlaufen.

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Die Spritze kann über eine rückwärtige Sperre verfügen, die sich am hinteren Ende des Spritzenkörpers befindet. Die rückwärtige Sperre kann aus der Spritze entfernbar sein. Verfügt der Spritzenkörper über terminale Ausleger an dem zum Auslass-Ende gegenüberliegenden Ende, kann die rückwärtige Sperre so konfiguriert werden, dass sie die terminalen Ausleger des Körpers im Wesentlichen umgibt, da dies eine Bewegung der rückwärtigen Sperre in eine Richtung parallel zur ersten Achse verhindert.

Der Stab kann über mindestens eine vom Auslass-Ende wegweisende Stabschulter verfügen, und die rückwärtige Sperre kann eine in Richtung des Auslass-Endes ausgerichtete Schulter der rückwärtigen Sperre aufweisen, um zusammen mit der Schulter des Stabes im Wesentlichen zu verhindern, dass sich der Stab vom Auslass-Ende entfernt, wenn sich die Schulter der rückwärtigen Sperre und die Stabschulter berühren. Eine Einschränkung der Bewegung des Stabes vom Auslass-Ende weg kann dabei helfen, Sterilität während der letzten Schritte des Sterilisationsvorgangs oder anderer Vorgänge aufrechtzuerhalten, bei denen sich der Druck innerhalb der variablen Volumenkammer und außerhalb der variablen Kammer verändern kann. Während solcher Vorgänge kann jegliches Gases, das in der variablen Volumenkammer eingeschlossen ist, oder können sich Blasen, die sich in einer darin befindlichen Flüssigkeit bilden können, im Volumen ändern und so verursachen, dass sich der Stopper bewegt. Die Bewegung des Stoppers weg vom Auslass könnte zur Aufbrechen eines durch den Stopper errichteten Sterilitätsbereichs führen. Dies ist besonders bei kleinvolumigen Spritzen wichtig, bei denen die Toleranzwerte bei den Bauteilgrößen viel enger gesteckt sind und der Stopper über eine geringere Flexibilität verfügt. Der Begriff Sterilitätsbereich, wie er hier verwendet wird, wird genutzt, um sich auf einen Bereich in der Spritze zu beziehen, der vom Stopper gegen das Eindringen von beiden Enden der Spritze abgedichtet wird. Dabei kann es sich um den Bereich zwischen einer Dichtung des Stoppers handeln, zum Beispiel einer umlaufenden Lamelle, welche sich am nächsten zum Auslass befindet, und einer Dichtung des Stoppers, zum Beispiel eine umlaufende Lamelle, welche am weitesten von Auslass entfernt ist. Die Entfernung zwischen diesen beiden Dichtungen bestimmt den Sterilitätsbereich des Stoppers, da der Stopper in einer sterilen Umgebung in die Spritzenzylinder eingebracht wird.

Um die Sterilität währende der oben genannten Vorgänge weiter aufrechtzuerhalten, kann der Stopper eine vordere umlaufende Lamelle und eine rückwärtige umlaufende Lamelle umfassen, und diese Lamellen können in einer Richtung entlang der ersten Achse durch einem Mindestabstand von 3 mm, 3,5 mm, 3,75 mm, 4 mm oder mehr getrennt voneinander sein. Eine oder mehrere zusätzliche Lamellen (zum Beispiel 2, 3, 4 oder 5 zusätzliche Lamellen, oder zwischen 1-10, 2-8, 3-6 oder 4-5 zusätzliche

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Lamellen) können zwischen den vorderen und hinteren Lamellen angeordnet sein. Gemäß einer Ausführungsform gibt es insgesamt drei umlaufende Lamellen.

Ein Stopper mit solch einem verbesserten Sterilitätsbereich kann auch einen Schutz für das injizierbare Medikament während eines letzten Sterilisationsverfahrens bieten. Weitere Lamellen am Stopper oder ein größerer Abstand zwischen den vorderen und hinteren Lamellen können die potentielle Exposition des Medikaments gegenüber dem sterilisierenden Mittel vermindern. Jedoch kann die zunehmende Lamellenanzahl die Reibung zwischen dem Stopper und dem Spritzenkörper erhöhen und somit die Handhabbarkeit herabsetzen. Während dies überwunden werden kann, indem man die Silikonisierung der Spritze erhöht, ist eine solche Erhöhung des Silikonöllevels bei Spritzen für den ophthalmischen Gebrauch besonders unerwünscht.

Die Stabschulter kann innerhalb des Außendurchmessers des Stabes oder außerhalb des Außendurchmessers des Stabes angeordnet werden. Durch das Bereitstellen einer Schulter, die sich über den Außendurchmesser des Stabes hinaus erstreckt, aber immer noch in den Körper passt, kann die Schulter dazu beitragen die Bewegung des Stabes im Körper zu stabilisieren, indem sie die Bewegung des Stabes senkrecht zur ersten Achse verringert. Die Stabschulter kann jedes dafür geeignete Element zum Bilden einer Schulter auf dem Stab umfassen, aber in einer Ausführungsform umfasst die Stabschulter einen im Wesentlichen scheibenförmigen Teil auf dem Stab.

In einer Ausführungsform der Spritze, bei der die Kolbenkontaktfläche den Stopper berührt und die variable Volumenkammer ihr vorgesehenes Maximalvolumen aufweist, gibt es einen Zwischenraum von nicht mehr als 2 mm zwischen der Stabschulter und der Schulter der rückwärtigen Sperre. In einigen Ausführungsformen beträgt der Zwischenraum weniger als etwa 1,5 mm und in einigen weniger als 1 mm. Dieser Abstand wird gewählt, um im Wesentlichen eine übermäßige Rückwärtsbewegung (vom Auslass-Ende weg) des Stoppers erheblich zu verringern oder zu verhindern.

In einer Ausführung hat die variable Volumenkammer einen Innendurchmesser von mehr als 5 mm oder 6 mm, oder weniger als 3 mm oder 4 mm. Der Innendurchmesser kann zwischen 3 mm und 6 mm, oder zwischen 4 mm und 5 mm betragen.

In einer anderen Ausführungsform ist die Spritze so dimensioniert, dass sie ein nominales maximales Füllvolumen zwischen etwa 0,1 ml und etwa 1,5 ml aufweist. Bei bestimmten Ausführungsformen liegt das nominale maximale Füllvolumen zwischen ungefähr 0.5 ml und ungefähr 1 ml. Bei bestimmten Ausführungsformen beträgt das nominale maximale Füllvolumen ungefähr 0,5 ml oder ungefähr 1 ml, oder ungefähr 1,5 ml.

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Die Länge des Spritzenkörpers kann weniger als 70 mm, weniger als 60 mm oder weniger als 50 mm betragen. In einer Ausführungsform liegt die Länge des Spritzenkörpers zwischen 45 mm und 50 mm.

In einer Ausführungsform ist die Spritze mit zwischen etwa 0,01 ml und etwa 1,5 ml (zum Beispiel zwischen etwa 0,05 ml und etwa 1 ml, zwischen etwa 0,1 ml und etwa 0,5 ml, zwischen etwa 0,15 ml und etwa 0,175 ml) einer VEGF-Antagonistenlösung gefüllt. Bei einer Ausführungsform ist die Spritze mit 0,165 ml einer VEGF-Antagonistenlösung gefüllt. Natürlich ist eine Spritze typischerweise mit mehr als der gewünschten Dosis, die dem Patienten verabreicht werden soll, gefüllt, um den Verlust aufgrund von „Totraums" in der Spritze und der Nadel zu berücksichtigen. Es kann auch ein gewisser Verlust auftreten, wenn die Spritze vom Behandelnden gefüllt wird, damit sie zur Verabreichung an den Patienten zur Verfügung steht.

Daher ist die Spritze in einer Ausführungsform mit einem Dosiervolumen (d. h. das für die Verabreichung an den Patienten vorgesehene Medikamentenvolumen) zwischen etwa 0,01 ml und etwa 1,5 ml (z. B. zwischen etwa 0,05 ml und etwa 1 ml, zwischen etwa 0,1 ml und etwa 0,5 ml) einer VEGF-Antagonistenlösung. In einer Ausführungsform liegt das Dosiervolumen zwischen etwa 0,03 ml und etwa 0,05 ml. Für Lucentis zum Beispiel beträgt das Dosiervolumen 0,05 ml oder 0,03 ml (0,5 mg oder 0,3 mg) einer 10 mg/ml injizierbaren Medikamentenlösung; für Eylea beträgt das Dosiervolumen 0,05 ml einer 40 mg/ml injizierbaren Medikamentenlösung. Obgleich Bevacizumab für ophthalmische Indikationen nicht zugelassen ist, wird es bei solchen ophthalmischen Indikationen in einer Konzentration von 25 mg/ml als *off-Label* (d.h. außerhalb der zugelassenen Indikation) angewandt; typischerweise mit einem Dosisvolumen von 0,05 ml (1,25 mg). Gemäß einer Ausführungsform beträgt das aus der Spritze extrahierbare Volumen (das ist die Menge des Produkts, die nach dem Befüllen aus der Spritze erhältlich ist, wobei ein Verlust aufgrund des Totvolumens in der Spritze und der Nadel berücksichtigt wird) etwa 0,09 ml.

In einer Ausführungsform ist der Spritzenkörper zwischen etwa 45 mm und etwa 50 mm lang, der Innendurchmesser liegt zwischen etwa 4 mm und etwa 5 mm, das Füllvolumen beträgt zwischen etwa 0,12 und etwa 0,3 ml und das Dosiervolumen liegt zwischen etwa 0,03 ml und etwa 0,05 ml.

Da die Spritze eine Medikamentenlösung enthält, kann der Auslass zur Aufrechterhaltung der Sterilität des Medikamentes reversibel abgedichtet sein. Diese Abdichtung kann durch die Verwendung einer Dichtungsvorrichtung erreicht werden, wie im Stand der Technik bekannt ist. Zum Beispiel das von Vetter Pharma International GmbH erhältliche OVS™-System.

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Typischerweise wird die Spritze silikonisiert, um eine leichte Handhabung zu ermöglichen, d. h. das Auftragen von Silikonöl auf die Innenseite des Zylinders, was die Kraft, die zum Bewegen des Stoppers aufgebracht werden muss, verringert. Für den ophthalmischen Gebrauch ist es jedoch wünschenswert, die Wahrscheinlichkeit, dass Silikonöltropfen ins Auge injiziert werden, zu senken. Durch mehrere Injektionen kann sich die Menge an Silikon-Tropfen im Auge aufbauen, wodurch mögliche unerwünschte Nebenwirkungen, einschließlich schwimmender Flocken (*Myodesopsia* oder „Floater") und einer Zunahme des intraokularen Drucks, verursacht werden können. Außerdem kann Silikonöl zur Aggregation von Proteinen führen. Eine typische 1 ml-Spritze umfasst 100 bis 800 µg Silikonöl im Zylinder, obgleich eine Befragung von Herstellern ergab, dass in vorgefüllten Spritzen typischerweise 500 bis 1000 µg verwendet wurden (Badkar *et al.* 2011, AAPS PharmaSciTech, 12(2): 564-572). Daher enthält eine Spritze gemäß der Erfindung in einer Ausführungsform weniger als etwa 800 µg (d. h. ungefähr weniger als etwa 500 µg, weniger als etwa 300 µg, weniger als etwa 200 µg, weniger als etwa 100 µg, weniger als etwa 75 µg, weniger als etwa 50 µg, weniger als etwa 25 µg, weniger als etwa 15 µg, weniger als etwa 10 µg) Silikonöl im Zylinder. Wenn die Spritze eine geringe Silikonmenge umfasst, kann dies mehr als etwa 1 µg, mehr als etwa 3 µg, mehr als etwa 5 µg, mehr als etwa 7 µg oder mehr als etwa 10 µg Silikonöl im Zylinder sein. Daher kann die Spritze gemäß einer Ausführungsform etwa 1 µg bis etwa 500 µg, etwa 3 µg bis etwa 200 µg, etwa 5 µg bis etwa 100 µg oder etwa 10 µg bis etwa 50 µg Silikonöl im Zylinder umfassen. Verfahren zur Messung der Silikonölmenge in solch einem Spritzenzylinder sind bereits im Stand der Technik bekannt und umfassen zum Beispiel unterschiedliche Wiegeverfahren und eine Quantifizierung durch Infrarotspektroskopie des mit einem geeigneten Lösungsmittel verdünnten Öls. Verschiedene Arten von Silikonöl sind verfügbar, aber typischerweise wird entweder DC 360 (Dow Corning®; mit einer Viskosität von 1000 cP) oder eine DC 365 Emulsion (Dow Corning®; DC 360-Öl mit einer Viskosität von 350 cP) für die Spritzensilikonisierung verwendet. In einer Ausführungsform enthält die vorgefüllte Spritze gemäß der Erfindung eine DC 365 Emulsion.

Bei Versuchen wurde überraschend herausgefunden, dass im Fall von Spritzen mit geringen Größen, wie die oben genannten, und vor allem denjenigen, die in Verbindung mit den unten stehenden Figuren beschrieben werden, die Losbrech- und Gleitkräfte für den Stopper in der Spritze weitgehend unbeeinträchtigt bleiben von einer Verminderung der Silikonierungsgrade weit unter die derzeitigen Standardwerte auf die hier genannten Levels. Dies steht im Gegensatz zur gebräuchlichen Denkweise, die zur Annahme führen würde, dass im Falle einer Verringerung des Silikonöllevels, die erforderlichen Kräfte zunehmen würden (siehe z.B. Schoenknecht, AAPS National Biotechnology

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Conference 2007 – Abstract Nr. NBC07-000488, worin gezeigt wird, dass 400 µg Silikonöl annehmbar sind, sich die Verwendbarkeit bei einem Anstieg des Silikonöls auf 800 µg aber verbessert. Eine zu hohe Kraft, die erforderlich wäre, um den Stopper zu bewegen, kann bei einigen Nutzern während des Gebrauchs zu Problemen führen, zum Beispiel könnte eine genaue Dosierungseinstellung oder eine gleichmäßige bzw. reibungslose Verabreichung der Dosis erschwert werden, falls viel Kraft von Nöten ist, um den Stopper in Bewegung zu setzen und/oder ihn in Bewegung zu halten. Eine gleichmäßige bzw. reibungslose Verabreichung ist bei empfindlichen Gewebearten, wie dem Auge, bei denen eine Bewegung der Spritze während der Verabreichung lokale Gewebeschäden verursachen könnte, besonders wichtig. Die Losbrech- und Gleitkräfte bei im Stand der Technik bekannten vorgefüllten Spritzen liegen typischerweise in der Größenordnung von unter 20 N, wobei aber vorgefüllte Spritzen ungefähr 100 µg bis ungefähr 800 µg Silikonöl enthalten. In einer Ausführungsform beträgt die Gleit-/Rutschkraft für den Stopper in der vorgefüllten Spritze weniger als etwa 11 N oder weniger als 9 N, weniger als 7 N, weniger als 5 N oder etwa 3 N bis 5 N. In einer Ausführungsform beträgt die Losbrechkraft weniger als etwa 11 N oder weniger als 9 N, weniger als 7 N, weniger als 5 N oder etwa 2 N bis 5 N. Es ist zu beachten, dass solche Messwerte eher für eine gefüllte Spritze gelten als für eine leere Spritze. Die Kräfte werden typischerweise an einem Stopper gemessen, der mit einer Geschwindigkeit von 190 mm/min bewegt wird. Gemäß einer Ausführungsform werden die Kräfte mit einer 30 G (Gauge) x 0,5 Inch Nadel, die auf die Spritze aufgesetzt ist, gemessen. In einer Ausführungsform verfügt die Spritze über ein nominales maximales Füllvolumen zwischen etwa 0,5 ml und 1 ml, beinhaltet weniger als etwa 100 µg Silikonöl, und die Losbrechkraft liegt zwischen etwa 2 N bis 5 N.

In einer Ausführungsform verfügt der Spritzenzylinder über eine Silikoninnenbeschichtung, die eine durchschnittliche Dicke von ungefähr 450 nm oder weniger (d.h. 400 nm oder weniger, 350 nm oder weniger, 300 nm oder weniger, 200 nm oder weniger, 100 nm oder weniger, 50 nm oder weniger, 20 nm oder weniger) hat. Verfahren zur Messung der Dicke der Silikonölschicht in einer Spritze sind im Stand der Technik bekannt und schließen die „rap.ID Layer Explorer®"-Anwendung ein, die auch genutzt werden kann, um die Silikonölmenge in einem Spritzenzylinder zu bestimmen. Gemäß einer weiteren Ausführungsform weist der Spritzenzylinder eine Innenbeschichtung von weniger als etwa 500 µg Silikonöl, vorzugsweise weniger als etwa 100 µg, vorzugsweise weniger als etwa 50 µg, vorzugsweise weniger als etwa 25 µg oder vorzugsweise weniger als etwa 10 µg Silikonöl auf.

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In einer Ausführungsform ist die Spritz frei oder nahezu frei von Silikonöl. Solch niedrige Silikonöllevels können erreicht werden, indem man unbeschichtete Spritzenzylinder verwendet und/oder die Verwendung von Silikonöl als ein Schmiermittel für Bauteile, die ein Produkt berühren, oder Pumpen bei dem Spritzenzusammenbau und der -befüllung vermeidet. Eine weitere Art, die Menge an Silikonöl und anorganischer Kieselsäure in einer vorgefüllten Spritze zu verringern, besteht darin, die Verwendung von silikonisierten Schläuchen bei der Befüllung, z.B. zwischen Lagertanks und Pumpen, zu vermeiden.

Die Spritze gemäß der Erfindung kann auch bestimmten Anforderungen beim Partikelgehalt gerecht werden. In einer Ausführungsform umfasst die ophthalmische Lösung nicht mehr als 2 Partikel von ≥ 50 µm im Durchmesser pro ml. In einer Ausführungsform umfasst die ophthalmische Lösung nicht mehr als 5 Partikel von ≥ 25 µm im Durchmesser pro ml. In einer Ausführungsform umfasst die ophthalmische Lösung nicht mehr als 50 Partikel von ≥ 10 µm im Durchmesser pro ml. In einer Ausführungsform umfasst die ophthalmische Lösung nicht mehr als 2 Partikel von ≥ 50 µm im Durchmesser pro ml, nicht mehr als 5 Partikel von ≥ 25 µm im Durchmesser pro ml und nicht mehr als 50 Partikel von ≥ 10 µm im Durchmesser pro ml. In einer Ausführungsform entspricht eine Spritze gemäß der Erfindung USP 789 (United States *Pharmacopoeia: Particulate Matter in Ophthalmic Solutions*). In einer Ausführungsform verfügt die Spritze über einen niedrigen Silikonöllevel, der ausreichend ist, damit die Spritze den Anforderungen von USP 789 entspricht.

**VEGF-Antagonisten**

*VEGF-Antikörper-Antagonisten*

VEGF ist ein gut beschriebenes Signalprotein, das die Angiogenese fördert. Zwei VEGF-Antikörper-Antagonisten wurden für die Nutzung beim Menschen zugelassen, nämlich Ranibizumab (Lucentis®) und Bevacizumab (Avastin®).

*Nicht-antikörperartige VEGF-Antagonisten*

In einem Aspekt der Erfindung ist ein nicht-antikörperartiger VEGF-Antagonist ein Immunoadhäsin. Solch ein Immunoadhäsin ist Aflibercept (Eylea®), das vor kurzem für die Nutzung beim Menschen zugelassen wurde und das auch als VEGF-Trap (Holash *et al.* (2002) PNAS USA 99:11393-98; Riely & Miller (2007) *Clin Cancer Res* 13:4623-7s) bekannt ist. Aflibercept ist der bevorzugte nicht-antikörperartige VEGF-Antagonist zur Verwendung mit der Erfindung. Aflibercept ist ein rekombinantes, humanes lösliches VEGF Rezeptor-Fusionsprotein, das aus Teilen der extrazellulären Domänen der humanen VEGF-Rezeptoren 1 und 2, fusioniert mit dem Fc-Teil des humanen IgG1

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besteht. Es ist ein dimeres Glycoprotein mit einem Proteinmolekulargewicht von 97 Kilodalton (kDA) und enthält Glycosylierungen, die zusätzliche 15 % der gesamten Molekularmasse ausmachen, was zu einem Gesamtmolekulargewicht von 115 kDa führt. Üblicherweise wird es als ein Glycoprotein durch Expression in rekombinanten CHO K1-Zellen erzeugt. Jedes Monomer kann die folgende Aminosäuresequenz (SEQ ID NO: 1) aufweisen:

SDTGRPFVEMYSEIPEIIHMTEGRELVIPCRVTSPNITVTLKKFPLDTLIPDGKRIIW
DSRKGFIISNATYKEIGLLTCEATVNGHLYKTNYLTHRQTNTIIDVVLSPSHGIELS
VGEKLVLNCTARTELNVGIDFNWEYPSSKHQHKKLVNRDLKTQSGSEMKKFLS
TLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHEKDKTHTCPPCPAPELLGG
PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP
REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE
PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD
SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

und Disulfidbrücken können zwischen den Resten 30-79, 124-185, 246-306 und 352-410 innerhalb jedes Monomers, und zwischen den Resten 211-211 und 214-214 zwischen den Monomeren gebildet werden.

Ein weiteres nicht-antikörperartiges VEGF-Antagonisten-Immunoadhäsin, das sich derzeit in der vorklinischen Entwicklung befindet, ist ein rekombinantes humanes lösliches VEGF-Rezeptor-Fusionsprotein, ähnlich von VEGF-Trap, welches extrazellulären Ligandenbindungsdomänen 3 und 4 aus VEGFR2/KDR und Domäne 2 aus VEGFR1/Flt-1 enthält; diese Domänen sind mit einem Proteinfragment des humanen IgG Fc fusioniert (Li et al., 2011 *Molecular Vision* 17:797-803). Dieser Antagonist bindet an die Isoformen VEGF-A, VEGF-B und VEGF-C. Das Molekül wird erzeugt, indem man zwei verschiedene Herstellungsverfahren nutzt, die zu unterschiedlichen Glycosylierungsmustern im fertigen Protein führen. Die zwei Glycoformen werden als KH902 (Conbercept) und KH906 bezeichnet. Das Fusionsprotein kann die folgende Aminosäuresequenz aufweisen (SEQ ID NO: 2):

MVSYWDTGVLLCALLSCLLLTGSSSGGRPFVEMYSEIPEIIHMTEGRELVIPCRV
TSPNITVTLKKFPLDTLIPDGKRIIWDSRKGFIISNATYKEIGLLTCEATVNGHLYKT
NYLTHRQTNTIIDVVLSPSHGIELSVGEKLVLNCTARTELNVGIDFNWEYPSSKH
QHKKLVNRDLKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTF
VRVHEKPFVAFGSGMESLVEATVGERVRLPAKYLGYPPPEIKWYKNGIPLESNH
TIKAGHVLTIMEVSERDTGNYTVILTNPISKEKQSHVVSLVVYVPPGPGDKTHTC
PLCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE

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KTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQP
ENNYKATPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK
SLSLSPGK

und wie VEGF-Trap als ein Dimer vorkommen. Dieses Fusionsprotein und damit verwandte Moleküle werden in EP1767546 genauer beschrieben.

Andere nicht-antikörperartige VEGF-Antagonisten umfassen Antikörper-Mimetika (z.B. Affibody®-Moleküle, Affiline, Affitine, Anticaline, Avimere, Kunitz-Domänenpeptide, und Monokörper) mit VEGF-Antagonistenaktivität. Dies schließt rekombinante Bindungsproteine ein, die eine Ankyrin-Wiederholungsdomäne umfassen, die VEGF-A bindet und hindert es daran, sich an VEGFR-2 zu binden. Ein Beispiel für solch ein Molekül ist DARPin® MP0112. Die Ankyrin-Bindungsdomäne kann die folgende Aminosäuresequenz haben (SEQ ID NO: 3):

GSDLGKKLLEAARAGQDDEVRILMANGADVNTADSTGWTPLHLAVPWGHLEIV
EVLLKYGADVNAKDFQGWTPLHLAAAIGHQEIVEVLLKNGADVNAQDKFGKTAF
DISIDNGNEDLAEILQKAA

Rekombinante Bindungsproteine, die eine Ankyrin-Wiederholungsdomäne umfassen, die VEGF-A bindet und daran hindert sich an VEGFR-2 zu binden, werden in WO2010/060748 und WO2011/135067 genauer beschrieben.

Weitere spezifische Antikörper-Mimetika mit einer VEGF-Antagonisten-Aktivität sind das 40 kD schwere pegylierte Anticalin PRS-050 und der Monokörper Angiocept (CT-322).

Der zuvor erwähnte nicht-antikörperartige VEGF-Antagonist kann modifiziert werden, um dessen pharmakokinetische Eigenschaften oder die Bioverfügbarkeit weiter zu verbessern. Zum Beispiel kann ein nicht-antikörperartiger VEGF-Antagonist chemisch modifiziert werden (z.B. pegyliert), um seine *in vivo* Halbwertszeit zu verlängern. Alternativ oder zusätzlich kann er durch Glykosylierung oder das Zufügen weiterer Glykosylierungsstellen modifiziert werden, die in der Proteinsequenz des natürlichen Proteins, von dem der VEGF-Antagonist abgeleitet wurde, nicht vorhanden sind.

Varianten des oben beschriebenen VEGF-Antagonisten, die verbesserte Eigenschaften für die erwünschte Anwendung aufweisen, können durch die Addition oder Deletion von Aminosäuren hergestellt werden. Gewöhnlich werden diese Aminosäuresequenzvarianten eine Aminosäuresequenz aufweisen, die zumindest 60% Aminosäure-Sequenzidentität mit der Aminosäuresequenz SEQ ID NO: 1, SEQ ID NO: 2 oder SEQ ID NO: 3, vorzugsweise zumindest 80%, weiter bevorzugt zumindest 85%, weiter bevorzugt zumindest 90% und am meisten bevorzugt zumindest 95% aufweisen, wobei z.B. 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%,

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93%, 94%, 95%, 96%, 97%, 98%, 99% und 100% eingeschlossen sind. Identität oder Homologie bezüglich dieser Sequenz wird hier definiert als der Prozentsatz der Aminosäurereste in der Kandidatensequenz, die mit SEQ ID 1, SEQ ID: 2 oder SEG ID NO: 3 identisch sind, nach einer Alignement-Anordnung der Sequenzen und einem Einführen von Lücken, falls erforderlich, um den maximalen Prozentsatz an Sequenzidentität zu erreichen, wobei jegliche konservativen Substitutionen als Teil der Sequenzidentität nicht berücksichtigt werden.

Sequenzidentität kann durch Standardverfahren bestimmt werden, die gewöhnlich verwendet werden, um die Ähnlichkeit der Position von Aminosäuren von zwei Polypeptiden zu vergleichen. Beim Verwenden eines Computerprogramms, wie BLAST oder FASTA, werden zwei Polypeptide durch Alignement angeordnet, um eine optimale Paarung der entsprechenden Aminosäuren zu erzielen (entweder entlang der vollständigen Länge einer oder beider Sequenzen oder entlang eines vorbestimmten Teils einer oder beider Sequenzen). Die Programme stellen standardmäßig einen Parameter für den Beginn (engl.: *opening penalty*) und standardmäßig einen Parameter für die Leerstellen (engl.: *gap penalty*) bereit, und eine Scoring-Matrize, wie PAM 250 [eine Standard-Scoring-Matrize; siehe Dayhoff *et al.*, in *„Atlas of Protein Sequence and Structure"*, Bd. 5, Ergänzungsband 3 (1978)], kann zusammen mit dem Computerprogramm verwendet werden. Zum Beispiel kann die prozentuale Identität anschließend berechnet werden: Die Gesamtanzahl identischer Paarungen multipliziert mit 100 und anschließend geteilt durch die Summe der Länge der längeren Sequenz innerhalb des gepaarten Bereichs und die Anzahl der Leerstellen, die in den längeren Sequenzen eingeführt sind, um die beiden Sequenzen durch ein Alignement anzuordnen.

Vorzugsweise bindet der nicht-antikörperartige VEGF-Antagonist gemäß der Erfindung an VEGF über eine oder mehrere Protein-Domäne(n), die nicht von der Antigen-Bindungsdomäne eines Antikörpers abgeleitet sind. Der nicht-antikörperartige VEGF-Antagonist gemäß der Erfindung ist vorzugsweise proteinös, kann aber Modifikationen einschließen, die nicht proteinös sind (z. B. Pegylierung, Glykosylierung).

**Therapie**

Die erfindungsgemäße Spritze kann verwendet werden, um eine Augenerkrankung zu behandeln, die eine choroidale Neovaskularisierung, eine altersbedingte Makuladegeneration (sowohl feuchte als auch trockene Formen), ein Makulaödem, das sekundär bei einem retinalen Gefäßverschluss (engl.: retinal vein occlusion; RVO) auftritt, einschließlich einem verzweigten RVO (engl.: branch RVO; bRVO) und einem zentralen RVO (engl.: central RVO; cRVO), eine choroidale Neovaskularisierung, die

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sekundär bei einer pathologischen Myopie auftritt (PM), ein diabetisches Makulaödem (DME), eine diabetische Retinopathie und eine proliferative Retinopathie einschließt, aber nicht darauf beschränkt ist.

Daher stellt die Erfindung ein Verfahren zum Behandeln eines Patienten bereit, der an einer Augenerkrankung leidet, die ausgewählt ist aus einer choroidalen Neovaskularisierung, einer feuchten altersbedingten Makuladegeneration, einem Makulaödem, das sekundär bei einem retinalen Gefäßverschluss (RVO) auftritt, einschließlich einem verzweigten RVO (BRVO) und einem zentralen RVO (cRVO), einer choroidalen Neovaskularisierung, die sekundär bei einer pathologische Myopie (PM), auftritt, einem diabetischem Makulaödem (DME), einer diabetischen Retinopathie und einer proliferativen Retinopathie, umfassend den Schritt des Verabreichens einer ophthalmischen Lösung an den Patienten unter Verwendung einer vorgefüllten Spritze gemäß der Erfindung. Dieses Verfahren umfasst vorzugsweise ferner einen einleitenden Befüllungsschritt, bei dem der Behandelnde den Kolben der vorgefüllten Spritze drückt, um den vorbestimmten Teil des Stoppers an der Füllmarkierung auszurichten.

In einer Ausführungsform stellt die Erfindung ein Verfahren bereit zur Behandlung einer Augenerkrankung, die ausgewählt ist aus einer choroidalen Neovaskularisierung, einer feuchten altersbedingten Makuladegeneration, einem Makulaödem, das sekundär bei einem retinalen Gefäßverschluss (RVO) auftritt, einschließlich einem verzweigtem RVO (bRVO) und einem zentralen RVO (cRVO), einer choroidalen Neovaskularisierung, die sekundär zu einer pathologische Myopie (PM) auftritt, einem diabetischen Makulaödem (DME), einer diabetischen Retinopathie und einer proliferativen Retinopathie, umfassend das Verabreichen eines nicht-antikörperartigen VEGF-Antagonisten mit einer vorgefüllten Spritze gemäß der Erfindung, wobei der Patient zuvor eine Behandlung mit einem VEGF-Antikörper-Antagonisten erhalten hat.

**Kits**

Ebenso werden Kits bereitgestellt, welche die vorgefüllten Spritzen gemäß der Erfindung umfassen. In einer Ausführungsform umfasst ein solches Kit eine vorgefüllte Spritze gemäß der Erfindung in einer Blisterpackung. Die Blisterpackung kann selbst auf der Innenseite steril sein. In einer Ausführungsform können Spritzen gemäß der Erfindung innerhalb solcher Blisterpackungen platziert werden, um eine Sterilisation zu durchlaufen, z. B. eine abschließende Sterilisation.

Ein solches Kit kann ferner eine Nadel zur Verabreichung des VEGF Antagonisten umfassen. Sofern der VEGF-Antagonist intravitreal verabreicht werden soll, ist es typisch eine Nadel mit 30-Gauge x ½ Inch zu verwenden, obgleich 31-Gauge und 32-Gauge

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Nadeln verwendet werden können. Für eine intravitreale Verabreichung könnten alternativ 33-Gauge oder 34-Gauge Nadeln verwendet werden. Solche Kits können ferner Gebrauchsanweisungen umfassen. In einer Ausführungsform stellt die Erfindung eine Schachtel bereit, die eine vorgefüllte Spritze gemäß der Erfindung enthält, die innerhalb einer Blisterpackung enthalten ist, eine Nadel und wahlweise Anleitungen zur Verabreichung.

**Sterilisation**

Wie oben angemerkt, kann ein abschließendes Sterilisationsverfahren verwendet werden, um die Spritze zu sterilisieren, und für ein solches Verfahren kann ein bekanntes Verfahren verwendet werden, wie ein Sterilisationsverfahren mittels Ethylenoxid (EtO) oder Wasserstoffperoxid ($H_2O_2$). Nadeln, die mit der Spritze verwendet werden sollen, können, wie auch erfindungsgemäße Kits, durch dasselbe Verfahren sterilisiert werden.

Die Packung wird dem sterilisierenden Gas ausgesetzt, bis die Außenseite der Spritze steril ist. Nach einem solchen Verfahren kann die äußere Oberfläche der Spritze (während sie in ihrer Blisterpackung ist) für bis zu 6 Monate, 9 Monate, 12 Monate, 15 Monate, 18 Monate, 24 Monate oder länger steril bleiben. Gemäß einer Ausführungsform kann eine Spritze gemäß der Erfindung daher (während sie sich in ihrer Blisterpackung befindet) eine Lagerungsbeständigkeit von bis zu 6 Monaten, 9 Monaten, 12 Monaten, 15 Monaten, 18 Monaten, 24 Monaten oder länger aufweisen. Gemäß einer Ausführungsform weist weniger als eine Spritze aus einer Million nachweisbar Mikroben an der Außenseite der Spritze nach 18 Monaten Lagerung auf. In einer Ausführungsform ist die vorgefüllte Spritze unter Verwendung von EtO mit einem Sterilitätssicherheitsgrad von mindestens $10^{-6}$ sterilisiert worden. In einer Ausführungsform ist die vorgefüllte Spritze unter Verwendung von Wasserstoffperoxid mit einem Sterilitätssicherheitsgrad von mindestens $10^{-6}$ sterilisiert worden. Selbstverständlich ist es ein Erfordernis, dass signifikante Mengen des sterilisierenden Gases nicht in die variable Volumenkammer der Spritze eindringen sollten. Der Begriff "signifikante Mengen", wie hier verwendet, bezieht sich auf eine Menge an Gas, die eine nicht akzeptable Veränderung der ophthalmischen Lösung innerhalb der variablen Volumenkammer verursachen würde. In einer Ausführungsform verursacht das Sterilisierungsverfahren ≤ 10 % (vorzugsweise ≤ 5 %, ≤ 3 %, ≤ 1 %) Alkylierung des VEGF-Antagonisten. In einer Ausführungsform ist die vorgefüllte Spritze unter Verwendung von EtO sterilisiert worden, aber die äußere Oberfläche der Spritze weist ≤ 1 ppm, vorzugsweise ≤ 0,2 ppm EtO Rest auf. In einer Ausführungsform ist die vorgefüllte Spritze unter Verwendung von Wasserstoffperoxid sterilisiert worden, aber die äußere Oberfläche der Spritze weist einen

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Wasserstoffperoxidrest von ≤ 1 ppm, vorzugsweise ≤ 0,2 ppm auf. In einer weiteren Ausführungsform ist die vorgefüllte Spritze unter Verwendung von EtO sterilisiert worden, und der gesamte EtO Rest, der auf der Außenseite der Spritze und der Innenseite der Blisterpackung gefunden wurde, beträgt ≤ 0,1 mg. In einer anderen Ausführungsform ist die vorgefüllte Spritze unter Verwendung von Wasserstoffperoxid sterilisiert worden, und der gesamte Wasserstoffperoxidrest, der auf der Außenseite der Spritze und der Innenseite der Blisterpackung gefunden wurde, beträgt ≤ 0,1 mg.

**Allgemeines**

Der Begriff "umfassend" bedeutet "einschließend" als auch "bestehend aus", z.B. kann eine Zusammensetzung, "umfassend" X, ausschließlich aus X bestehen oder sie kann etwas Zusätzliches einschließen, z.B. X + Y.

Der Begriff "etwa" in Bezug auf einen numerischen Wert *x* bedeutet z. B. *x* ± 10%.

Eine Bezugnahme auf eine prozentuale Sequenzidentität zwischen zwei Aminosäuresequenzen bedeutet, dass bei einer Alignement-Anordnung dieser Prozentsatz der Aminosäuren beim Vergleich der zwei Sequenzen derselbe bzw. identisch ist. Diese Alignement-Anordnung und die prozentuale Homologie oder Sequenzidentität kann unter Verwendung von Software-Programmen bestimmt werden, die im Stand der Technik bekannt sind, zum Beispiel jene, die in Abschnitt 7.7.18 der *Current Protocols in Molecular Biology* (F. M. Ausubel *et al.*, Hrsg., 1987) Ergänzungsband 30 beschrieben sind. Eine bevorzugte Alignement-Anordnung wird durch den Smith-Waterman Homologiesuche-Algorithmus unter Verwendung einer affinen Leerlückensuche mit einem *gap open penalty*-Parameter von 12 und einem *gap extension penalty*-Parameter von 2, einer BLOSUM-Matrize von 62 bestimmt. Der Smith-Waterman Homologiesuche-Algorithmus wird in Smith & Waterman (1981) *Adv. Appl. Math.* 2: 482-489 offenbart.

**KURZE BESCHREIBUNG DER FIGUREN**

Figur 1 zeigt eine Seitenansicht einer Spritze.

Figur 2 zeigt einen Querschnitt einer Spritze in einer Ansicht von oben nach unten.

Figur 3 zeigt eine Ansicht eines Kolbens.

Figur 4 zeigt einen Querschnitt durch einen Kolben.

Figur 5 zeigt einen Stopper.

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**FORMEN ZUR AUSFÜHRUNG DER ERFINDUNG**

Die Erfindung wird nachfolgend lediglich exemplarisch mit Bezugnahme auf die Zeichnungen weiter beschrieben.

Figur 1 zeigt eine Ansicht von einer Seite einer Spritze 1 umfassend einen Körper 2, einen Kolben 4, eine rückwärtige Sperre 6 und eine Abdichtvorrichtung 8.

Figur 2 zeigt einen Querschnitt durch die Spritze 1 von Figur 1 von oben. Die Spritze 1 ist zur Verwendung mit einer ophthalmischen Injektion geeignet. Die Spritze 1 umfasst einen Körper 2, einen Stopper 10 und einen Kolben 4. Die Spritze 1 erstreckt sich entlang einer ersten Achse A. Der Körper 2 umfasst einen Auslass 12 an einem Auslass-Ende 14, und der Stopper 10 ist derart innerhalb von Körper 2 angeordnet, dass eine frontale Oberfläche 16 des Stoppers 10 und der Körper 2 eine variable Volumenkammer 18 definieren. Die variable Volumenkammer 18 enthält ein injizierbares Medikament 20, das eine ophthalmische Lösung umfasst, die einen VEGF-Antagonisten umfasst, wie Ranibizumab. Die injizierbare Lösung 20 kann durch den Auslass 12 mittels einer Bewegung des Stoppers 10 auf das Auslass-Ende 14 hin, herausgedrückt werden, wodurch sich das Volumen der variablen Volumenkammer 18 verringert. Der Kolben 4 umfasst eine Kolbenkontaktfläche 22 an einem ersten Ende 24 und einen Stab 26, der sich zwischen der Kolbenkontaktfläche 22 und einem hinteren Teil 25 erstreckt. Die Kolbenkontaktfläche 22 ist derart angeordnet, dass sie den Stopper 10 berührt, sodass der Kolben 4 dazu verwendet werden kann, um dem Stopper 10 auf das Auslass-Ende 14 des Körpers 2 zu zubewegen. Eine derartige Bewegung verringert das Volumen der variablen Volumenkammer 18 und verursacht, dass die Flüssigkeit darin, durch den Auslass heraus gedrückt wird.

Die rückwärtige Sperre 6 schließt sich an den Körper 2 an durch eine Kopplung an einen terminalen Ausleger 28 des Körpers 2. Die rückwärtige Sperre 6 schließt einen Verbundteil 30 ein, der derart gestaltet ist, um im Wesentlichen zumindest einen Teil des terminalen Auslegers 28 des Körpers 2 zu umgeben. Die rückwärtige Sperre 6 ist derart gestaltet, um an den Körper 2 von der Seite angekoppelt zu werden, indem eine Seite der rückwärtigen Sperre 6 offen bleibt, sodass die rückwärtige Sperre 6 an der Spritze 2 angebracht werden kann.

Der Körper 2 definiert eine im Wesentlichen zylindrische Bohrung 36, die einen Bohrungsradius aufweist. Der Stab 26 umfasst eine Stabschulter 32, die vom Auslass-Ende 14 weg weist. Die Stabschulter 32 erstreckt sich bis zu einem Stabschulterradius der ersten Achse A, der so ausgebildet ist, dass er geringfügig kleiner ist, als der Bohrungsradius, sodass die Schulter in die Bohrung 36 passt. Die rückwärtige Sperre 6

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schließt eine Schulter 34 der rückwärtigen Sperre ein, die auf das Auslass-Ende 14 hin ausgerichtet ist. Die Schultern 32, 34 sind derart gestaltet, dass sie zusammen im Wesentlichen eine Bewegung des Stabs 26 weg vom Auslass-Ende 14 verhindern, wenn die Schulter 34 der rückwärtigen Sperre und die Stabschulter 32 sich berühren. Die Schulter 34 der rückwärtigen Sperre erstreckt sich von außerhalb des Bohrungsradius bis zu einem Radius, der geringer ist, als der Radius der Stabschulter, sodass die Stabschulter 32 die Schulter 34 der rückwärtigen Sperre nicht durch eine Bewegung entlang der ersten Achse A übergehen kann. In diesem Fall ist die Stabschulter 32 im Wesentlichen scheiben- oder ringförmig, und die Schulter 34 der rückwärtigen Sperre schließt einen Bogen um das hintere Ende 38 des Körpers 2 ein.

Die rückwärtige Sperre 6 schließt auch zwei fingerförmige Vorsprünge 40 ein, die sich in entgegengesetzte Richtungen weg vom Körper 2 im Wesentlichen senkrecht zur ersten Achse A erstrecken, um eine manuelle Handhabung der Spritze 1 während der Verwendung zu erleichtern.

In diesem Beispiel umfasst die Spitze einen 0, 5 ml-Körper 2, der mit zwischen etwa 0,1 und 0,3 ml eines injizierbaren Medikaments 20 gefüllt ist, das eine 10mg/ml injizierbare Lösung umfasst, welche Ranibizumab umfasst. Der Spritzenkörper 2 hat einen inneren Durchmesser von zwischen etwa 4,5 mm und 4,8 mm, eine Länge von zwischen etwa 45 mm und 50 mm.

Der Kolben 4 und Stopper 10 werden unter Bezugnahme auf die nachfolgende Figuren detaillierter beschrieben.

Figur 3 zeigt eine perspektivische Ansicht des Kolbens 4 von Figur 1, wobei die Kolbenkontaktfläche 22 am ersten Ende 24 des Kolbens 4 gezeigt ist. Der Stab 26 erstreckt sich vom ersten Ende 24 des hinteren Teils 25. Der hintere Teil 25 schließt einen scheibenförmigen Ausleger 42 ein, um die Handhabung der Vorrichtung durch den Verwender zu erleichtern. Der Ausleger 42 stellt einen größeren Oberflächenbereich zur Berührung durch den Verwender bereit als ein bloßes Ende des Stabs 26.

Figur 4 zeigt einen Querschnitt durch einen Spritzenkörper 2 und einen Stab 26. Der Stab 26 schließt vier längsverlaufende Lamellen 44 ein, und der Winkel zwischen den Lamellen beträgt 90°.

Figur 5 zeigt eine detaillierte Ansicht eines Stoppers 10, wobei eine konisch geformte frontale Oberfläche 16 und drei umlaufende Lamellen 52, 54, 56 um einen im Wesentlichen zylindrischen Körper 58 gezeigt sind. Die axiale Lücke zwischen der ersten Lamelle 52 und der letzten Lamelle 56 beträgt etwa 3 mm. Die hinter Oberfläche 60 des Stoppers 10 schließt eine im Wesentlichen zentrale Aussparung 62 ein. Die zentrale

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Aussparung 62 schießt eine Anfangsbohrung 64 mit einem ersten Durchmesser ein. Die Anfangsbohrung 64 führt von der hinteren Oberfläche 60 in den Stopper 10 zu einer inneren Aussparung 66 mit einem zweiten Durchmesser, der zweite Durchmesser ist größer als der erste Durchmesser.

**Stopperbewegungskräfte**

0,5 ml Spritzen silikonisiert mit < 100 µg Silikonöl, gefüllt mit Lucentis, die eine von zwei unterschiedlichen Stoppergestaltungen umfassen, wurden auf ihre maximale Losbrech- und Gleitkraft getestet. Vor dem Testen wurden 30 G x 0,5" Nadeln an den Spritzen angebracht. Das Testen wurde bei einer Stoppergeschwindigkeit von 190 mm/min über eine Weglänge von 10,9 mm durchgeführt. Die Stoppergestaltung 2 weist eine Zunahme des Abstands zwischen der vorderen umlaufenden Lamelle und der hinteren umlaufenden Lamelle von 45% auf.

| | | Stoppergestaltung 1 | | | Stoppergestaltung 2 | |
|---|---|---|---|---|---|---|
| | | Charge A | Charge B | Charge C | Charge D | Charge E |
| Losbrechkraft von Spritzen | Mittelwert von 10 Spritzen | 2.2 N | 2.3N | 1.9 N | 2.1 N | 2.5 N |
| | Maximaler Einzelwert | 2.5 N | 2.5N | 2.3 N | 2.6 N | 2.7 N |
| Gleitkraft | Mittelwert von 10 Spritzen | 3.1 N | 3.2 N | 3.1 N | 4.1 N | 4.6 N |
| | Maximaler Einzelwert | 3.5 N | 3.5 N | 3.6 N | 4.7 N | 4.8 N |

Für beide Stoppergestaltungen blieb die durchschnittliche und maximale Losbrechkraft unter 3N. Für beide Stoppergestaltungen blieb die durchschnittliche und maximale Gleitkraft unter 5N.Es versteht sich, dass die Erfindung lediglich exemplarisch beschrieben worden ist und Modifikationen ausgeführt werden können, die innerhalb des Schutzbereichs und Geistes der Erfindung bleiben.

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**Schutzansprüche**

1. Eine vorgefüllte Spritze, wobei die Spritze einen Körper, einen Stopper und einen Kolben umfasst,

der Körper umfasst einen Auslass an einem Auslass-Ende, und der Körper ist aus Glas hergestellt,

der Stopper ist derart innerhalb des Körpers angeordnet, dass eine frontale Oberfläche des Stoppers und der Körper eine variable Volumenkammer beschreiben, aus der eine Flüssigkeit durch den Auslass gedrückt werden kann,

der Kolben umfasst eine Kolbenkontaktfläche an einem ersten Ende und einen Stab, der sich zwischen der Kolbenkontaktfläche und einem hinteren Anteil erstreckt,

die Kolbenkontaktfläche ist angeordnet, um den Stopper zu berühren, sodass der Kolben dazu verwendet werden kann, den Stopper zum Auslass-Ende des Körpers hin zu drücken, wobei das Volumen der variablen Volumenkammer reduziert wird,

die Flüssigkeit ist eine ophthalmische Lösung, die einen VEGF-Antagonisten umfasst, und

(a) die Spritze weist ein nominales maximales Füllvolumen zwischen etwa 0,5 ml und etwa 1 ml auf,

(b) das Dosisvolumen beträgt etwa 0,05 ml der VEGF-Antagonisten-Lösung,

(c) die Spritze umfasst eine geringe Menge Silikonöl,

(d) die VEGF-Antagonisten-Lösung umfasst nicht mehr als zwei Partikel von ≥ 50 µm im Durchmesser pro ml, und

(e) der VEGF-Antagonist ist der nicht-antikörperartige VEGF-Antagonist Aflibercept in einer Konzentration von 40 mg/ml.

2. Eine vorgefüllte Spritze gemäß Anspruch 1, wobei die Spritze mit zwischen etwa 0,15 ml und etwa 0,175 ml der VEGF-Antagonisten-Lösung gefüllt ist.

3. Eine vorgefüllte Spritze gemäß einem der vorhergehenden Ansprüche, wobei die Spritze mit etwa 0,165 ml der VEGF-Antagonisten-Lösung gefüllt ist.

4. Eine vorgefüllte Spritze gemäß einem der vorhergehenden Ansprüche, wobei der Spritzenzylinder eine Innenbeschichtung aus Silikonöl mit einer durchschnittlichen Dicke von etwa 450 nm oder weniger aufweist.

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5. Eine vorgefüllte Spritze gemäß einem der vorhergehenden Ansprüche, wobei der Spritzenzylinder eine Innenbeschichtung aus Silikonöl mit einer durchschnittlichen Dicke von 400 nm oder weniger aufweist.

6. Eine vorgefüllte Spritze gemäß einem der vorhergehenden Ansprüche, wobei der Spritzenzylinder eine Innenbeschichtung aus Silikonöl mit einer durchschnittlichen Dicke von 350 nm oder weniger aufweist.

7. Eine vorgefüllte Spritze gemäß einem der vorhergehenden Ansprüche, wobei der Spritzenzylinder eine Innenbeschichtung aus Silikonöl mit einer durchschnittlichen Dicke von 300 nm oder weniger aufweist.

8. Eine vorgefüllte Spritze gemäß einem der vorhergehenden Ansprüche, wobei der Spritzenzylinder eine Innenbeschichtung aus Silikonöl mit einer durchschnittlichen Dicke von 200 nm oder weniger aufweist.

9. Eine vorgefüllte Spritze gemäß einem der vorhergehenden Ansprüche, wobei der Spritzenzylinder eine Innenbeschichtung aus Silikonöl mit einer durchschnittlichen Dicke von 100 nm oder weniger aufweist.

10. Eine vorgefüllte Spritze gemäß einem der vorhergehenden Ansprüche, wobei der Spritzenzylinder eine Innenbeschichtung aus Silikonöl mit einer durchschnittlichen Dicke von 50 nm oder weniger aufweist.

11. Eine vorgefüllte Spritze gemäß einem der vorhergehenden Ansprüche, wobei der Spritzenzylinder eine Innenbeschichtung aus Silikonöl mit einer durchschnittlichen Dicke von 20 nm oder weniger aufweist.

12. Eine vorgefüllte Spritze gemäß einem der vorhergehenden Ansprüche, wobei die Spritze weniger als etwa 500 µg Silikonöl im Zylinder umfasst.

13. Eine vorgefüllte Spritze gemäß einem der vorhergehenden Ansprüche, wobei die Spritze weniger als etwa 300 µg Silikonöl im Zylinder umfasst.

14. Eine vorgefüllte Spritze gemäß einem der vorhergehenden Ansprüche, wobei die Spritze weniger als etwa 200 µg Silikonöl im Zylinder umfasst.

15. Eine vorgefüllte Spritze gemäß einem der vorhergehenden Ansprüche, wobei die Spritze weniger als etwa 100 µg Silikonöl im Zylinder umfasst.

16. Eine vorgefüllte Spritze gemäß einem der vorhergehenden Ansprüche, wobei die Spritze weniger als etwa 75 µg Silikonöl im Zylinder umfasst.

17. Eine vorgefüllte Spritze gemäß einem der vorhergehenden Ansprüche, wobei die Spritze weniger als etwa 50 µg Silikonöl im Zylinder umfasst.

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18. Eine vorgefüllte Spritze gemäß einem der vorhergehenden Ansprüche, wobei die Spritze weniger als etwa 25 µg Silikonöl im Zylinder umfasst.

19. Eine vorgefüllte Spritze gemäß einem der vorhergehenden Ansprüche, wobei die Spritze weniger als etwa 15 µg Silikonöl im Zylinder umfasst.

20. Eine vorgefüllte Spritze gemäß einem der vorhergehenden Ansprüche, wobei die Spritze weniger als etwa 10 µg Silikonöl im Zylinder umfasst.

21. Eine vorgefüllte Spritze gemäß einem der vorhergehenden Ansprüche, wobei das Silikonöl eine DC 365 Emulsion ist.

22. Eine vorgefüllte Spritze gemäß einem der vorhergehenden Ansprüche, wobei die VEGF-Antagonisten-Lösung ferner (i) nicht mehr als 5 Partikel von ≥ 25 µm im Durchmesser pro ml und/oder (ii) nicht mehr als 50 Partikel von ≥ 10 µm im Durchmesser pro ml umfasst.

23. Eine vorgefüllte Spritze gemäß einem der vorhergehenden Ansprüche, wobei die VEGF-Antagonisten-Lösung USP 789 entspricht.

24. Eine vorgefüllte Spritze gemäß einem der vorhergehenden Ansprüche, wobei die Spritze eine Stopperlosbrechkraft von weniger als etwa 11 N aufweist.

25. Eine vorgefüllte Spritze gemäß Anspruch 24, wobei die Spritze eine Stopperlosbrechkraft von weniger als etwa 5 N aufweist.

26. Eine vorgefüllte Spritze gemäß Anspruch 24 oder 25, wobei die Spritze eine Stopperlosbrechkraft zwischen etwa 2 N und 5 N aufweist.

27. Eine vorgefüllte Spritze gemäß einem der vorhergehenden Ansprüche, wobei die Spritze eine Stoppergleitkraft von weniger als etwa 11 N aufweist.

28. Eine vorgefüllte Spritze gemäß Anspruch 27, wobei die Spritze eine Stoppergleitkraft von weniger als etwa 5 N aufweist.

29. Eine vorgefüllte Spritze gemäß Anspruch 27 oder 28, wobei die Spritze eine Stoppergleitkraft zwischen etwa 3 N und 5 N aufweist.

30. Eine vorgefüllte Spritze gemäß einem der vorhergehenden Ansprüche, bei der das Dosisvolumen durch das Volumen der variablen Volumenkammer bestimmt ist, wenn ein vorbestimmter Teil des Stoppers oder Kolbens an einer Füllmarke auf der Spritze ausgerichtet ist.

31. Eine Blisterpackung, umfassend eine vorgefüllte Spritze gemäß einem der vorhergehenden Ansprüche, wobei die Spritze unter Verwendung von EtO sterilisiert worden ist.

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32. Eine Blisterpackung, umfassend eine vorgefüllte Spritze gemäß einem der vorhergehenden Ansprüche, wobei die Spritze unter Verwendung von $H_2O_2$ sterilisiert worden ist.

33. Eine Blisterpackung, umfassend eine vorgefüllte Spritze gemäß Anspruch 31, wobei die äußere Oberfläche der Spritze einen EtO Rest von ≤ 1 ppm aufweist.

34. Eine Blisterpackung, umfassend eine vorgefüllte Spritze gemäß Anspruch 32, wobei die äußere Oberfläche der Spritze einen $H_2O_2$ Rest von ≤ 1 ppm aufweist.

35. Eine Blisterpackung, umfassend eine vorgefüllte Spritze gemäß Anspruch 31, wobei die Spritze unter Verwendung von EtO sterilisiert worden ist und der gesamte EtO Rest, der auf der Außenseite der Spritze und der Innenseite der Blisterpackung gefunden wird, ≤ 0,1 mg beträgt.

36. Eine Blisterpackung, umfassend eine vorgefüllte Spritze gemäß Anspruch 32, wobei die Spritze unter Verwendung von $H_2O_2$ sterilisiert worden ist und der gesamte $H_2O_2$ Rest, der auf der Außenseite der Spritze und der Innenseite der Blisterpackung gefunden wird, ≤ 0,1 mg beträgt.

37. Eine Blisterpackung, umfassend eine vorgefüllte Spritze gemäß einem der Ansprüche 31, 33 oder 35, wobei ≤ 5 % des VEGF-Antagonisten alkyliert sind.

38. Eine Blisterpackung, umfassend eine vorgefüllte Spritze gemäß einem der Ansprüche 31, 33, 35 oder 37, wobei die Spritze unter Verwendung von EtO mit einem Sterilitätssicherheitsgrad von mindestens $10^{-6}$ sterilisiert worden ist.

39. Eine Blisterpackung, umfassend eine vorgefüllte Spritze gemäß einem der Ansprüche 32, 34 oder 36, wobei die Spritze unter Verwendung von $H_2O_2$ mit einem Sterilitätssicherheitsgrad von mindestens $10^{-6}$ sterilisiert worden ist.

40. Eine Blisterpackung gemäß einem der Ansprüche 31 bis 39, wobei die vorgefüllte Spritze eine Lagerungsbeständigkeit von bis zu 6 Monaten, 9 Monaten, 12 Monaten, 15 Monaten, 18 Monaten, 24 Monaten oder länger aufweist.

41. Ein Kit umfassend: (i) eine vorgefüllte Spritze gemäß einem der Ansprüche 1 bis 30 oder eine Blisterpackung, umfassend eine vorgefüllte Spritze gemäß einem der Ansprüche 31 bis 40, (ii) eine Nadel, und wahlweise (iii) Anleitungen zur Verabreichung.

42. Ein Kit gemäß Anspruch 41, wobei die Nadel eine 30 Gauge x 0,5 Inch Nadel ist.

43. Eine vorgefüllte Spritze gemäß einem der Ansprüche 1 bis 30 zur Verwendung in der Therapie.

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44. Eine vorgefüllte Spritze gemäß einem der Ansprüche 1 bis 30 zur Verwendung in der Behandlung einer Augenerkrankung, ausgewählt aus choroidaler Neovaskularisierung, feuchter altersbedingter Makuladegeneration, Makulaödem, sekundär bei einem retinalen Gefäßverschluss (RVO), einschließlich einem verzweigten RVO (bRVO) und einem zentralen RVO (cRVO), choroidaler Neovaskularisierung, sekundär bei einer pathologischen Myopie (PM), diabetischem Makulaödem (DME), diabetischer Retinopathie und proliferativer Retinopathie.

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1/1

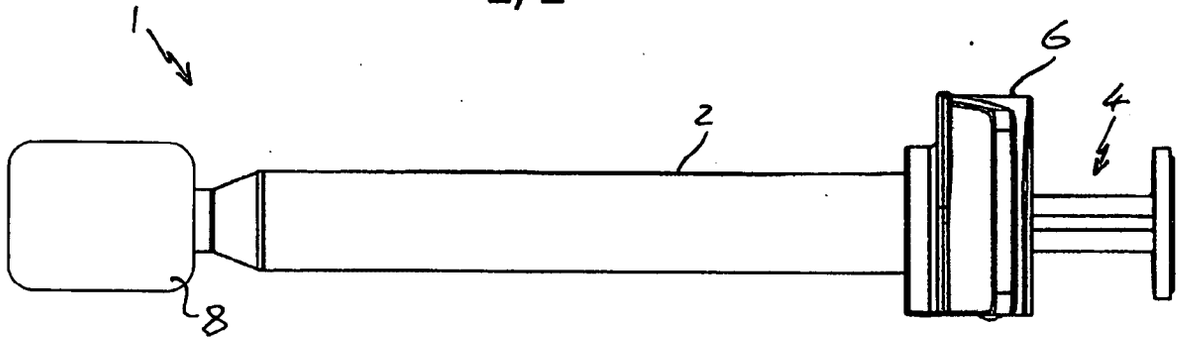


Fig 1

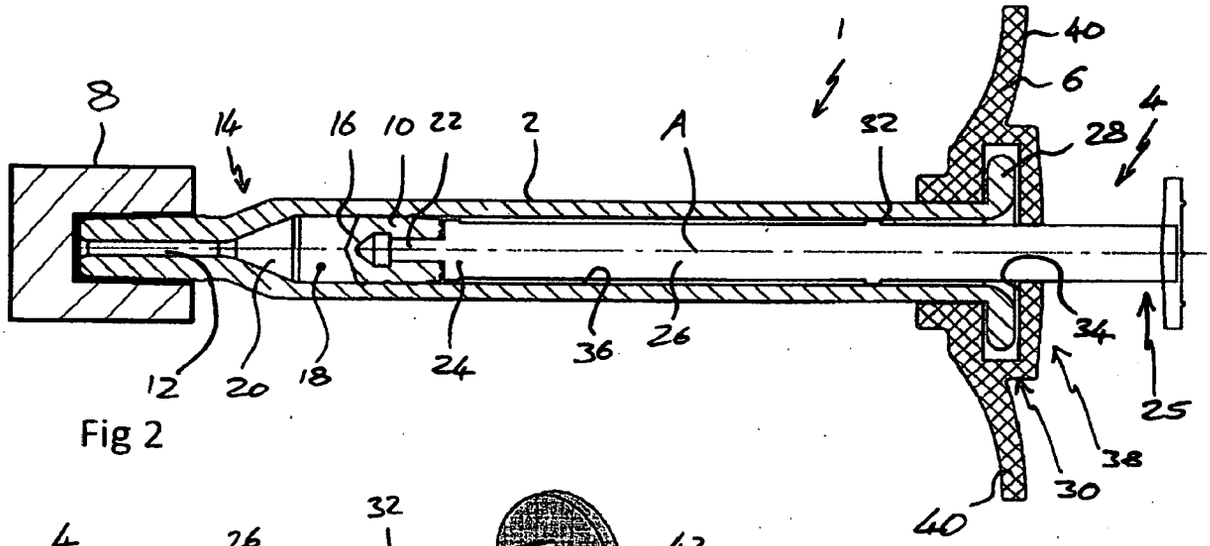


Fig 2

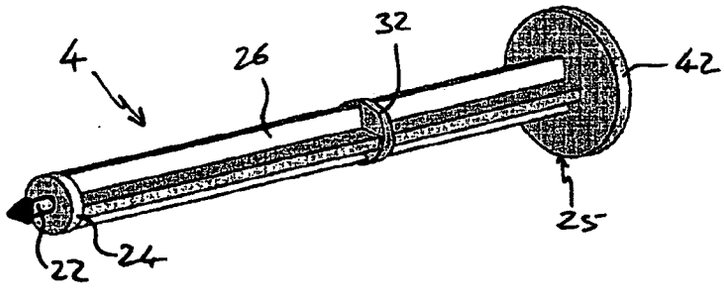


Fig 3

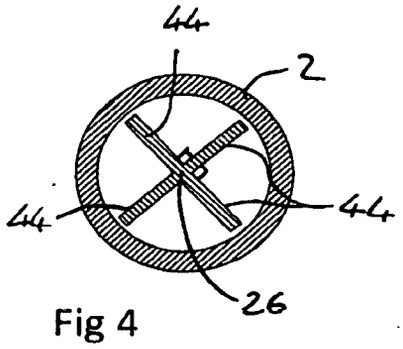


Fig 4

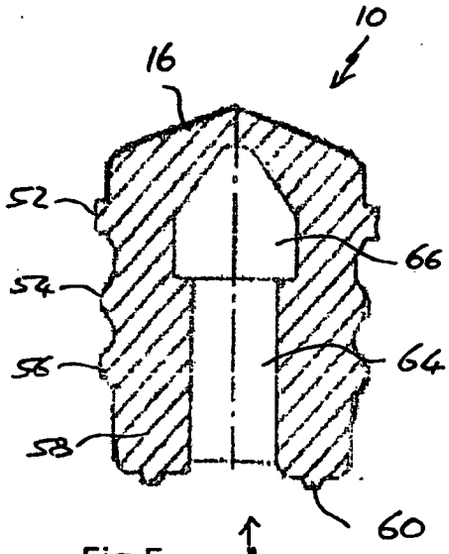


Fig 5

DocCode – SCORE

## SCORE Placeholder Sheet for IFW Content

Application Number: **13750352** Filing Date: **03/15/2013**

The presence of this form in the IFW record indicates that the following document is stored in the SCORE database

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I, ALITA CLARK, PATENT AND PLANT BREEDERS RIGHTS ADMINISTRATION (PPBRA) hereby certify that annexed is a true copy of the Complete specification in connection with Innovation Patent No. 2013100071 for a patent by NOVARTIS AG as filed on 23 January 2013.

WITNESS my hand this
Nineteenth day of February 2013

ALITA CLARK
PATENT AND PLANT BREEDERS
RIGHTS ADMINISTRATION (PPBRA)

COMMONWEALTH OF AUSTRALIA
AUSTRALIA
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PAT055157-AU-Innovation3

# DEVICE

## TECHNICAL FIELD

The present invention relates to a syringe, particularly to a small volume syringe such as a syringe suitable for ophthalmic injections.

## BACKGROUND ART

Many medicaments are delivered to a patient in a syringe from which the user can dispense the medicament. If medicament is delivered to a patient in a syringe it is often to enable the patient, or a caregiver, to inject the medicament. It is important for patient safety and medicament integrity that the syringe and the contents of that syringe are sufficiently sterile to avoid infection, or other, risks for patients. Sterilisation can be achieved by terminal sterilisation in which the assembled product, typically already in its associated packaging, is sterilised using heat or a sterilising gas.

For small volume syringes, for example those for injections into the eye in which it is intended that about 0.1ml or less of liquid is to be injected the sterilisation can pose difficulties that are not necessarily associated with larger syringes. Changes in pressure, internal or external to the syringe, can cause parts of the syringe to move unpredictably, which may alter sealing characteristics and potentially compromise sterility. Incorrect handling of the syringe can also pose risks to product sterility.

Furthermore, certain therapeutics such as biologic molecules are particularly sensitive to sterilisation, be it cold gas sterilisation, thermal sterilisation, or irradiation. Thus, a careful balancing act is required to ensure that while a suitable level of sterilisation is carried out, the syringe remains suitably sealed, such that the therapeutic is not compromised. Of course, the syringe must also remain easy to use, in that the force required to depress the plunger to administer the medicament must not be too high.

There is therefore a need for a new syringe construct which provides a robust seal for its content, but which maintains ease of use.

## DISCLOSURE OF THE INVENTION

The present invention provides a pre-filled syringe, the syringe comprising a body, a stopper and a plunger, the body comprising an outlet at an outlet end and the stopper being arranged within

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the body such that a front surface of the stopper and the body define a variable volume chamber from which a fluid can be expelled though the outlet, the plunger comprising a plunger contact surface at a first end and a rod extending between the plunger contact surface and a rear portion, the plunger contact surface arranged to contact the stopper, such that the plunger can be used to force the stopper towards the outlet end of the body, reducing the volume of the variable volume chamber, characterised in that the fluid comprises an ophthalmic solution. In one embodiment, the ophthalmic solution comprises a VEGF-antagonist.

In one embodiment, the syringe is suitable for ophthalmic injections, more particularly intravitreal injections, and as such has a suitably small volume. The syringe may also be silicone oil free, or substantially silicone oil free, or may comprise a low level of silicone oil as lubricant. In one embodiment, despite the low silicone oil level, the stopper break loose and slide force is less than 20N.

For ophthalmic injections, it is particularly important for the ophthalmic solution to have particularly low particle content. In one embodiment, the syringe meets US Pharmacopeia standard 789 (USP789).

***Syringe***

The body of the syringe may be a substantially cylindrical shell, or may include a substantially cylindrical bore with a non circular outer shape. The outlet end of the body includes an outlet through which a fluid housed within the variable volume chamber can be expelled as the volume of said chamber is reduced. The outlet may comprise a projection from the outlet end through which extends a channel having a smaller diameter than that of the variable volume chamber. The outlet may be adapted, for example via a luer lock type connection, for connection to a needle or other accessory such as a sealing device which is able to seal the variable volume chamber, but can be operated, or removed, to unseal the variable volume chamber and allow connection of the syringe to another accessory, such as a needle. Such a connection may be made directly between the syringe and accessory, or via the sealing device. The body extends along a first axis from the outlet end to a rear end.

The body may be made from a plastic material (e.g. a cyclic olefin polymer) or from glass and may include indicia on a surface thereof to act as an injection guide. In one embodiment the body may comprise a priming mark. This allows the physician to align a pre-determined part of the stopper (such as the tip of the front surface or one of the circumferential ribs, discussed later)

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or plunger with the mark, thus expelling excess ophthalmic solution and any air bubbles from the syringe. The priming process ensures that an exact, pre-determined dosage is administered to the patient.

The stopper may be made from rubber, silicone or other suitable resiliently deformable material. The stopper may be substantially cylindrical and the stopper may include one or more circumferential ribs around an outer surface of the stopper, the stopper and ribs being dimensioned such that the ribs form a substantially fluid tight seal with an internal surface of the syringe body. The front surface of the stopper may be any suitable shape, for example substantially planar, substantially conical or of a domed shape. The rear surface of the stopper may include a substantially central recess. Such a central recess could be used to connect a plunger to the stopper using a snap fit feature or thread connection in a known manner. The stopper may be substantially rotationally symmetric about an axis through the stopper.

The plunger comprises a plunger contact surface and extending from that a rod extends from the plunger contact surface to a rear portion. The rear portion may include a user contact portion adapted to be contacted by a user during an injection event. The user contact portion may comprise a substantially disc shaped portion, the radius of the disc extending substantially perpendicular to the axis along which the rod extends. The user contact portion could be any suitable shape. The axis along which the rod extends may be the first axis, or may be substantially parallel with the first axis.

The syringe may include a backstop arranged at a rear portion of the body. The backstop may be removable from the syringe. If the syringe body includes terminal flanges at the end opposite the outlet end the backstop may be configured to substantially sandwich terminal flanges of the body as this prevent movement of the backstop in a direction parallel to the first axis.

The rod may comprise at least one rod shoulder directed away from the outlet end and the backstop may include a backstop shoulder directed towards the outlet end to cooperate with the rod shoulder to substantially prevent movement of the rod away from the outlet end when the backstop shoulder and rod shoulder are in contact. Restriction of the movement of the rod away from the outlet end can help to maintain sterility during terminal sterilisation operations, or other operations in which the pressure within the variable volume chamber or outside the chamber may change. During such operations any gas trapped within the variable volume chamber, or bubbles that may form in a liquid therein, may change in volume and thereby cause the stopper to move. Movement of the stopper away from the outlet could result in the breaching of a

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sterility zone created by the stopper. This is particularly important for low volume syringes where there are much lower tolerances in the component sizes and less flexibility in the stopper. The term sterility zone as used herein is used to refer to the area within the syringe that is sealed by the stopper from access from either end of the syringe. This may be the area between a seal of the stopper, for example a circumferential rib, closest to the outlet and a seal of the stopper, for example a circumferential rib, furthest from the outlet. The distance between these two seals defines the sterility zone of the stopper since the stopper is installed into the syringe barrel in a sterile environment.

To further assist in maintaining sterility during the operations noted above the stopper may comprise at a front circumferential rib and a rear circumferential rib and those ribs may be separated in a direction along the first axis by at least 3mm, by at least 3.5 mm, by at least 3.75mm or by 4mm or more. One or more additional ribs (for example 2, 3, 4 or 5 additional ribs, or between 1-10, 2-8, 3-6 or 4-5 additional ribs) may be arranged between the front and rear ribs. In one embodiment there are a total of three circumferential ribs.

A stopper with such an enhanced sterility zone can also provide protection for the injectable medicament during a terminal sterilisation process. More ribs on the stopper, or a greater distance between the front and rear ribs can reduce the potential exposure of the medicament to the sterilising agent. However, increasing the number of ribs can increase the friction between the stopper and syringe body, reducing ease of use. While this may be overcome by increasing the siliconisation of the syringe, such an increase in silicone oil levels is particularly undesirable for syringes for ophthalmic use.

The rod shoulder may be arranged within the external diameter of the rod, or may be arranged outside the external diameter of the rod. By providing a shoulder that extends beyond the external diameter of the rod, but still fits within the body, the shoulder can help to stabilise the movement of the rod within the body by reducing movement of the rod perpendicular to the first axis. The rod shoulder may comprise any suitable shoulder forming elements on the rod, but in one embodiment the rod shoulder comprises a substantially disc shaped portion on the rod.

In one embodiment of the syringe, when arranged with the plunger contact surface in contact with the stopper and the variable volume chamber is at its intended maximum volume there is a clearance of no more than about 2mm between the rod shoulder and backstop shoulder. In some embodiments there is a clearance of less than about 1.5 mm and in some less than about 1mm.

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This distance is selected to substantially limit or prevent excessive rearward (away from the outlet end) movement of the stopper.

In one embodiment the variable volume chamber has an internal diameter greater than 5mm or 6mm, or less than 3mm or 4mm. The internal diameter may be between 3mm and 6mm, or between 4mm and 5mm.

In another embodiment the syringe is dimensioned so as to have a nominal maximum fill volume of between about 0.1ml and about 1.5ml. In certain embodiments the nominal maximum fill volume is between about 0.5ml and about 1ml. In certain embodiments the nominal maximum fill volume is about 0.5ml or about 1ml, or about 1.5ml.

The length of the body of the syringe may be less than 70mm, less than 60mm or less than 50mm. In one embodiment the length of the syringe body is between 45mm and 50mm.

In one embodiment, the syringe is filled with between about 0.01ml and about 1.5ml (for example between about 0.05ml and about 1ml, between about 0.1ml and about 0.5ml, between about 0.15ml and about 0.175ml) of a VEGF antagonist solution. In one embodiment, the syringe is filled with 0.165ml of a VEGF antagonist solution. Of course, typically a syringe is filled with more than the desired dose to be administered to the patient, to take into account wastage due to "dead space" within the syringe and needle. There may also be a certain amount of wastage when the syringe is primed by the physician, so that it is ready to inject the patient.

Thus, in one embodiment, the syringe is filled with a dosage volume (i.e. the volume of medicament intended for delivery to the patent) of between about 0.01ml and about 1.5ml (e.g. between about 0.05ml and about 1ml, between about 0.1ml and about 0.5ml) of a VEGF antagonist solution. In one embodiment, the dosage volume is between about 0.03ml and about 0.05ml. For example, for Lucentis, the dosage volume is 0.05ml or 0.03ml (0.5mg or 0.3mg) of a 10mg/ml injectable medicament solution; for Eylea, the dosage volume is 0.05ml of a 40mg/ml injectable medicament solution. Although unapproved for ophthalmic indications, bevacizumab is used off-label in such ophthalmic indications at a concentration of 25mg/ml; typically at a dosage volume of 0.05ml (1.25mg). In one embodiment, the extractable volume from the syringe (that is the amount of product obtainable from the syringe following filling, taking into account loss due to dead space in the syringe and needle) is about 0.09ml.

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In one embodiment the length of the syringe body is between about 45mm and about 50mm, the internal diameter is between about 4mm and about 5mm, the fill volume is between about 0.12 and about 0.3ml and the dosage volume is between about 0.03ml and about 0.05ml.

As the syringe contains a medicament solution, the outlet may be reversibly sealed to maintain sterility of the medicament. This sealing may be achieved through the use of a sealing device as is known in the art. For example the OVS™ system which is available from Vetter Pharma International GmbH.

It is typical to siliconise the syringe in order to allow ease of use, i.e. to apply silicone oil to the inside of the barrel, which decreases the force required to move the stopper. However, for ophthalmic use, it is desirable to decrease the likelihood of silicone oil droplets being injected into the eye. With multiple injections, the amount of silicone droplets can build up in the eye, causing potential adverse effects, including "floaters" and an increase in intra-ocular pressure. Furthermore, silicone oil can cause proteins to aggregate. A typical 1ml syringe comprises 100-800µg silicone oil in the barrel, though a survey of manufacturers reported that 500-1000µg was typically used in pre-filled syringes (Badkar *et al.* 2011, AAPS PharmaSciTech, 12(2):564-572). Thus, in one embodiment, a syringe according to the invention comprises less than about 800µg (i.e. about less than about 500µg, less than about 300µg, less than about 200µg, less than about 100µg, less than about 75µg, less than about 50µg, less than about 25µg, less than about 15µg, less than about 10µg) silicone oil in the barrel. If the syringe comprises a low level of silicone oil, this may be more than about 1µg, more than about 3µg, more than about 5µg, more than about 7µg or more than about 10µg silicone oil in the barrel. Thus, in one embodiment, the syringe may comprise about 1µg-about 500µg, about 3µg-about 200µg, about 5µg-about 100µg or about 10µg-about 50µg silicone oil in the barrel. Methods for measuring the amount of silicone oil in such a syringe barrel are known in the art and include, for example, differential weighing methods and quantitation by infrared-spectroscopy of the oil diluted in a suitable solvent. Various types of silicone oil are available, but typically either DC360 (Dow Corning®; with a viscosity of 1000cP) or DC365 emulsion (Dow Corning®; DC360 oil with a viscosity of 350cP) are used for syringe siliconisation. In one embodiment, the pre-filled syringe of the invention comprises DC365 emulsion.

During testing it was surprisingly found that, for syringes having small dimensions, such as those discussed above, and particularly those described in conjunction with the Figures below, the break loose and sliding forces for the stopper within the syringe are substantially unaffected by

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reducing the siliconisation levels far below the current standard to the levels discussed here. This is in contrast to conventional thinking that would suggest that if you decrease the silicone oil level, the forces required would increase (see e.g. Schoenknecht, AAPS National Biotechnology Conference 2007 – Abstract no. NBC07-000488, which indicates that while 400µg silicone oil is acceptable, usability improves when increased to 800µg). Having too great a force required to move the stopper can cause problems during use for some users, for example accurate dose setting or smooth dose delivery may be made more difficult if significant strength is required to move, and/or keep in motion, the stopper. Smooth administration is particularly important in sensitive tissues such as the eye, where movement of the syringe during administration could cause local tissue damage. Break loose and slide forces for pre-filled syringes known in the art are typically in the region of less than 20N, but where the pre-filled syringes contain about 100µg-about 800µg silicone oil. In one embodiment the glide/slide force for the stopper within the pre-filled syringe is less than about 11N or less than 9N, less than 7N, less than 5N or between about 3N to 5N. In one embodiment, the break loose force is less than about 11N or less than 9N, less than 7N, less than 5N or between about 2N to 5N. Note that such measurements are for a filled syringe, rather than an empty syringe. The forces are typically measured at a stopper travelling speed of 190mm/min. In one embodiment, the forces are measured with a 30G x 0.5 inch needle attached to the syringe. In one embodiment, the syringe has a nominal maximal fill volume of between about 0.5ml and 1ml, contains less than about 100µg silicone oil and has a break loose force between about 2N to 5N.

In one embodiment the syringe barrel has an internal coating of silicone oil that has an average thickness of about 450nm or less (i.e. 400nm or less, 350nm or less, 300nm or less, 200nm or less, 100nm or less, 50nm or less, 20nm or less). Methods to measure the thickness of silicone oil in a syringe are known in the art and include the rap.ID Layer Explorer® Application, which can also be used to measure the mass of silicone oil inside a syringe barrel.

In one embodiment, the syringe is silicone oil free, or substantially silicone oil free. Such low silicone oil levels can be achieved by using uncoated syringe barrels and/or by avoiding the use of silicone oil as a lubricant for product contacting machine parts, or pumps in the syringe assembly and fill line. A further way to reduce silicone oil and inorganic silica levels in a pre-filled syringe is to avoid the use of silicone tubing in filling lines, for example between storage tanks and pumps.

The syringe according to the invention may also meet certain requirements for particulate content. In one embodiment, the ophthalmic solution comprises no more than 2 particles ≥50μm in diameter per ml. In one embodiment, the ophthalmic solution comprises no more than 5 particles ≥25μm in diameter per ml. In one embodiment, the ophthalmic solution comprises no more than 50 particles ≥10μm in diameter per ml. In one embodiment, the ophthalmic solution comprises no more than 2 particles ≥50μm in diameter per ml, no more than 5 particles ≥25μm in diameter per ml and no more than 50 particles ≥10μm in diameter per ml. In one embodiment, a syringe according to the invention meets USP789 (United States Pharmacopoeia: Particulate Matter in Ophthalmic Solutions). In one embodiment the syringe has low levels of silicone oil sufficient for the syringe to meet USP789.

***VEGF Antagonists***

*Antibody VEGF antagonists*

VEGF is a well-characterised signal protein which stimulates angiogenesis. Two antibody VEGF antagonists have been approved for human use, namely ranibizumab (Lucentis®) and bevacizumab (Avastin®).

*Non-Antibody VEGF antagonists*

In one aspect of the invention, the non-antibody VEGF antagonist is an immunoadhesin. One such immuoadhesin is aflibercept (Eylea®), which has recently been approved for human use and is also known as VEGF-trap (Holash *et al.* (2002) *PNAS USA* 99:11393-98; Riely & Miller (2007) *Clin Cancer Res* 13:4623-7s). Aflibercept is the preferred non-antibody VEGF antagonist for use with the invention. Aflibercept is a recombinant human soluble VEGF receptor fusion protein consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1. It is a dimeric glycoprotein with a protein molecular weight of 97 kilodaltons (kDa) and contains glycosylation, constituting an additional 15% of the total molecular mass, resulting in a total molecular weight of 115 kDa. It is conveniently produced as a glycoprotein by expression in recombinant CHO K1 cells. Each monomer can have the following amino acid sequence (SEQ ID NO: 1):

SDTGRPFVEMYSEIPEIIHMTEGRELVIPCRVTSPNITVTLKKFPLDTLIPDGKRIIWDSRKGFIISNATY
KEIGLLTCEATVNGHLYKTNYLTHRQTNTIIDVVLSPSHGIELSVGEKLVLNCTARTELNVGIDFNWEYPS
SKHQHKKLVNRDLKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHEKDKTHTCPP
CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST
YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVK

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GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL
SLSPG

and disulfide bridges can be formed between residues 30-79, 124-185, 246-306 and 352-410 within each monomer, and between residues 211-211 and 214-214 between the monomers.

Another non-antibody VEGF antagonist immunoadhesin currently in pre-clinical development is a recombinant human soluble VEGF receptor fusion protein similar to VEGF-trap containing extracellular ligand-binding domains 3 and 4 from VEGFR2/KDR, and domain 2 from VEGFR1/Flt-1; these domains are fused to a human IgG Fc protein fragment (Li et al., 2011 *Molecular Vision* 17:797-803). This antagonist binds to isoforms VEGF-A, VEGF-B and VEGF-C. The molecule is prepared using two different production processes resulting in different glycosylation patterns on the final proteins. The two glycoforms are referred to as KH902 (conbercept) and KH906. The fusion protein can have the following amino acid sequence (SEQ ID NO:2):

MVSYWDTGVLLCALLSCLLLTGSSSGGRPFVEMYSEIPEIIHMTEGRELVIPCRVTSPNITVTLKKFPLDT
LIPDGKRIIWDSRKGFIISNATYKEIGLLTCEATVNGHLYKTNYLTHRQTNTIIDVVLSPSHGIELSVGEK
LVLNCTARTELNVGIDFNWEYPSSKHQHKKLVNRDLKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSG
LMTKKNSTFVRVHEKPFVAFGSGMESLVEATVGERVRLPAKYLGYPPPEIKWYKNGIPLESNHTIKAGHVL
TIMEVSERDTGNYTVILTNPISKEKQSHVVSLVVYVPPGPGDKTHTCPLCPAPELLGGPSVFLFPPKPKDT
LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC
KVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
ATPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

and, like VEGF-trap, can be present as a dimer. This fusion protein and related molecules are further characterized in EP1767546.

Other non-antibody VEGF antagonists include antibody mimetics (*e.g.* Affibody® molecules, affilins, affitins, anticalins, avimers, Kunitz domain peptides, and monobodies) with VEGF antagonist activity. This includes recombinant binding proteins comprising an ankyrin repeat domain that binds VEGF-A and prevents it from binding to VEGFR-2. One example for such a molecule is DARPin® MP0112. The ankyrin binding domain may have the following amino acid sequence (SEQ ID NO: 3):

GSDLGKKLLEAARAGQDDEVRILMANGADVNTADSTGWTPLHLAVPWGHLEIVEVLLKYGADVNAKDFQGW
TPLHLAAAIGHQEIVEVLLKNGADVNAQDKFGKTAFDISIDNGNEDLAEILQKAA

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Recombinant binding proteins comprising an ankyrin repeat domain that binds VEGF-A and prevents it from binding to VEGFR-2 are described in more detail in WO2010/060748 and WO2011/135067.

Further specific antibody mimetics with VEGF antagonist activity are the 40 kD pegylated anticalin PRS-050 and the monobody angiocept (CT-322).

The afore-mentioned non-antibody VEGF antagonist may be modified to further improve their pharmacokinetic properties or bioavailability. For example, a non-antibody VEGF antagonist may be chemically modified (e.g., pegylated) to extend its *in vivo* half-life. Alternatively or in addition, it may be modified by glycosylation or the addition of further glycosylation sites not present in the protein sequence of the natural protein from which the VEGF antagonist was derived.

Variants of the above-specified VEGF antagonists that have improved characteristics for the desired application may be produced by the addition or deletion of amino acids. Ordinarily, these amino acid sequence variants will have an amino acid sequence having at least 60% amino acid sequence identity with the amino acid sequences of SEQ ID NO: 1, SEQ ID NO: 2 or SEQ ID NO: 3, preferably at least 80%, more preferably at least 85%, more preferably at least 90%, and most preferably at least 95%, including for example, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, and 100%. Identity or homology with respect to this sequence is defined herein as the percentage of amino acid residues in the candidate sequence that are identical with SEQ ID NO: 1, SEQ ID NO: 2 or SEQ ID NO: 3, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity.

Sequence identity can be determined by standard methods that are commonly used to compare the similarity in position of the amino acids of two polypeptides. Using a computer program such as BLAST or FASTA, two polypeptides are aligned for optimal matching of their respective amino acids (either along the full length of one or both sequences or along a pre-determined portion of one or both sequences). The programs provide a default opening penalty and a default gap penalty, and a scoring matrix such as PAM 250 [a standard scoring matrix; see Dayhoff et al., in Atlas of Protein Sequence and Structure, vol. 5, supp. 3 (1978)] can be used in conjunction with the computer program. For example, the percent identity can then be calculated as: the total number of identical matches multiplied by 100 and then divided by the

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sum of the length of the longer sequence within the matched span and the number of gaps introduced into the longer sequences in order to align the two sequences.

Preferably, the non-antibody VEGF antagonist of the invention binds to VEGF via one or more protein domain(s) that are not derived from the antigen-binding domain of an antibody. The non-antibody VEGF antagonist of the invention are preferably proteinaceous, but may include modifications that are non-proteinaceous (e.g., pegylation, glycosylation).

***Therapy***

The syringe of the invention may be used to treat an ocular disease, including but not limited to choroidal neovascularisation, age-related macular degeneration (both wet and dry forms), macular edema secondary to retinal vein occlusion (RVO) including both branch RVO (bRVO) and central RVO (cRVO), choroidal neovascularisation secondary to pathologic myopia (PM), diabetic macular edema (DME), diabetic retinopathy, and proliferative retinopathy.

Thus the invention provides a method of treating a patient suffering from of an ocular disease selected from choroidal neovascularisation, wet age-related macular degeneration, macular edema secondary to retinal vein occlusion (RVO) including both branch RVO (bRVO) and central RVO (cRVO), choroidal neovascularisation secondary to pathologic myopia (PM), diabetic macular edema (DME), diabetic retinopathy, and proliferative retinopathy, comprising the step of administering an ophthalmic solution to the patient using a pre-filled syringe of the invention. This method preferably further comprises an initial priming step in which the physician depresses the plunger of the pre-filled syringe to align the pre-determined part of the stopper with the priming mark.

In one embodiment, the invention provides a method of treating an ocular disease selected from choroidal neovascularisation, wet age-related macular degeneration, macular edema secondary to retinal vein occlusion (RVO) including both branch RVO (bRVO) and central RVO (cRVO), choroidal neovascularisation secondary to pathologic myopia (PM), diabetic macular edema (DME), diabetic retinopathy, and proliferative retinopathy, comprising administering a non-antibody VEGF antagonist with a pre-filled syringe of the invention, wherein the patient has previously received treatment with an antibody VEGF antagonist.

***Kits***

Also provided are kits comprising the pre-filled syringes of the invention. In one embodiment, such a kit comprises a pre-filled syringe of the invention in a blister pack. The blister pack may

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itself be sterile on the inside. In one embodiment, syringes according to the invention may be placed inside such blister packs prior to undergoing sterilisation, for example terminal sterilisation.

Such a kit may further comprise a needle for administration of the VEGF antagonist. If the VEGF antagonist is to be administered intravitreally, it is typical to use a 30-gauge x ½ inch needle, though 31-gauge and 32-gauge needles may be used. For intravitreal administration, 33-gauge or 34-gauge needles could alternatively be used. Such kits may further comprise instructions for use. In one embodiment, the invention provides a carton containing a pre-filled syringe according to the invention contained within a blister pack, a needle and optionally instructions for administration.

***Sterilisation***

As noted above, a terminal sterilisation process may be used to sterilise the syringe and such a process may use a known process such as an ethylene oxide (EtO) or a hydrogen peroxide ($H_2O_2$) sterilisation process. Needles to be used with the syringe may be sterilised by the same method, as may kits according to the invention.

The package is exposed to the sterilising gas until the outside of the syringe is sterile. Following such a process, the outer surface of the syringe may remain sterile (whilst in its blister pack) for up to 6 months, 9 months, 12 months, 15 months, 18 months, 24 months or longer. Thus, in one embodiment, a syringe according to the invention (whilst in its blister pack) may have a shelf life of up to 6 months, 9 months, 12 months, 15 months, 18 months, 24 months or longer. In one embodiment, less than one syringe in a million has detectable microbial presence on the outside of the syringe after 18 months of storage. In one embodiment, the pre-filled syringe has been sterilised using EtO with a Sterility Assurance Level of at least $10^{-6}$. In one embodiment, the pre-filled syringe has been sterilised using hydrogen peroxide with a Sterility Assurance Level of at least $10^{-6}$. Of course, it is a requirement that significant amounts of the sterilising gas should not enter the variable volume chamber of the syringe. The term "significant amounts" as used herein refers to an amount of gas that would cause unacceptable modification of the ophthalmic solution within the variable volume chamber. In one embodiment, the sterilisation process causes ≤10% (preferably ≤5%, ≤3%, ≤1%) alkylation of the VEGF antagonist. In one embodiment, the pre-filled syringe has been sterilised using EtO, but the outer surface of the syringe has ≤1ppm, preferably ≤0.2ppm EtO residue. In one embodiment, the pre-filled syringe has been sterilised using hydrogen peroxide, but the outer surface of the syringe has ≤1ppm, preferably ≤0.2ppm

hydrogen peroxide residue. In another embodiment, the pre-filled syringe has been sterilised using EtO, and the total EtO residue found on the outside of the syringe and inside of the blister pack is ≤0.1mg. In another embodiment, the pre-filled syringe has been sterilised using hydrogen peroxide, and the total hydrogen peroxide residue found on the outside of the syringe and inside of the blister pack is ≤0.1mg.

***General***

The term "comprising" means "including" as well as "consisting" *e.g.* a composition "comprising" X may consist exclusively of X or may include something additional *e.g.* X + Y.

The term "about" in relation to a numerical value *x* means, for example, *x*±10%.

References to a percentage sequence identity between two amino acid sequences means that, when aligned, that percentage of amino acids are the same in comparing the two sequences. This alignment and the percent homology or sequence identity can be determined using software programs known in the art, for example those described in section 7.7.18 of *Current Protocols in Molecular Biology* (F.M. Ausubel *et al.*, eds., 1987) Supplement 30. A preferred alignment is determined by the Smith-Waterman homology search algorithm using an affine gap search with a gap open penalty of 12 and a gap extension penalty of 2, BLOSUM matrix of 62. The Smith-Waterman homology search algorithm is disclosed in Smith & Waterman (1981) *Adv. Appl. Math.* 2: 482-489

## BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows a side view of a syringe

Figure 2 shows a cross section of a top down view of a syringe

Figure 3 shows a view of a plunger

Figure 4 shows a cross section though a plunger

Figure 5 shows a stopper

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**MODES FOR CARRYING OUT THE INVENTION**

The invention will now be further described, by way of example only, with reference to the drawings.

Figure 1 shows a view from a side of a syringe 1 comprising a body 2, plunger 4, backstop 6 and a sealing device 8.

Figure 2 shows a cross section through the syringe 1 of Figure 1 from above. The syringe 1 is suitable for use in an ophthalmic injection. The syringe 1 comprises a body 2, a stopper 10 and a plunger 4. The syringe 1 extends along a first axis A. The body 2 comprises an outlet 12 at an outlet end 14 and the stopper 10 is arranged within the body 2 such that a front surface 16 of the stopper 10 and the body 2 define a variable volume chamber 18. The variable volume chamber 18 contains an injectable medicament 20 comprising an ophthalmic solution comprising a VEGF antagonist such as ranibizumab. The injectable fluid 20 can be expelled though the outlet 12 by movement of the stopper 10 towards the outlet end 14 thereby reducing the volume of the variable volume chamber 18. The plunger 4 comprises a plunger contact surface 22 at a first end 24 and a rod 26 extending between the plunger contact surface 22 and a rear portion 25. The plunger contact surface 22 is arranged to contact the stopper 10, such that the plunger 4 can be used to move the stopper 10 towards the outlet end 14 of the body 2. Such movement reduces the volume of the variable volume chamber 18 and causes fluid therein to be expelled though the outlet.

The backstop 6 is attached to the body 2 by coupling to a terminal flange 28 of the body 2. The backstop 6 includes sandwich portion 30 which is adapted to substantially sandwich at least some of the terminal flange 28 of the body 2. The backstop 6 is adapted to be coupled to the body 2 from the side by leaving one side of the backstop 6 open so that the backstop 6 can be fitted to the syringe 2.

The body 2 defines a substantially cylindrical bore 36 which has a bore radius. The rod 26 comprises a rod shoulder 32 directed away from the outlet end 14. The rod shoulder 32 extends from to a rod shoulder radius from the first axis A which is such that it is slightly less than the bore radius so that the shoulder fits within the bore 36. The backstop 6 includes a backstop shoulder 34 directed towards the outlet end 14. The shoulders 32, 34 are configured to cooperate to substantially prevent movement of the rod 26 away from the outlet end 14 when the backstop shoulder 34 and rod shoulder 32 are in contact. The backstop shoulder 34 extends from outside the bore radius to a radius less than the rod shoulder radius so that the rod shoulder 32 cannot pass the

backstop shoulder 34 by moving along the first axis A. In this case the rod shoulder 32 is substantially disc, or ring, shaped and the backstop shoulder 34 includes an arc around a rear end 38 of the body 2.

The backstop 6 also includes two finger projections 40 which extend in opposite directions away from the body 2 substantially perpendicular to the first axis A to facilitate manual handling of the syringe 1 during use.

In this example the syringe comprises a 0.5ml body 2 filled with between about 0.1 and 0.3 ml of an injectable medicament 20 comprising a 10mg/ml injectable solution comprising ranibizumab. The syringe body 2 has an internal diameter of about between about 4.5mm and 4.8mm, a length of between about 45mm and 50mm.

The plunger 4 and stopper 10 will be described in more detail with reference to later figures.

Figure 3 shows a perspective view of the plunger 4 of Figure 1 showing the plunger contact surface 22 at the first end 24 of the plunger 4. The rod 26 extends from the first end 24 to the rear portion 25. The rear portion 25 includes a disc shaped flange 42 to facilitate user handling of the device. The flange 42 provides a larger surface area for contact by the user than a bare end of the rod 26.

Figure 4 shows a cross section though a syringe body 2 and rod 26. The rod 26 includes four longitudinal ribs 44 and the angle between the ribs is 90°.

Figure 5 shows a detailed view of a stopper 10 showing a conical shaped front surface 16 and three circumferential ribs 52,54,56 around a substantially cylindrical body 58. The axial gap between the first rib 52 and the last rib 56 is about 3mm. The rear surface 60 of the stopper 10 includes a substantially central recess 62. The central recess 62 includes an initial bore 64 having a first diameter. The initial bore 64 leading from the rear surface 60 into the stopper 10 to an inner recess 66 having a second diameter, the second diameter being larger than the first diameter.

***Stopper movement forces***

0.5ml syringes siliconised with <100µg silicone oil, filled with Lucentis, comprising one of two different stopper designs were tested for maximal and average break out and slide force. Prior to testing, 30G x 0.5" needles were attached to the syringes. The testing was carried out at a stopper speed of 190mm/min over a travel length of 10.9mm. Stopper design 2 had a 45% increase in the distance between the front circumferential rib and rear circumferential rib.

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| | | Stopper design 1 | | | Stopper design 2 | |
|---|---|---|---|---|---|---|
| | | Batch A | Batch B | Batch C | Batch D | Batch E |
| Break loose force of syringes | Average of 10 syringes | 2.2N | 2.3N | 1.9N | 2.1N | 2.5N |
| | Max individual value | 2.5N | 2.5N | 2.3N | 2.6N | 2.7N |
| Sliding force | Average of 10 syringes | 3.1N | 3.2N | 3.1N | 4.1N | 4.6N |
| | Max individual value | 3.5N | 3.5N | 3.6N | 4.7N | 4.8N |

For both stopper designs, average and maximum break out force remained below 3N. For both stopper designs, average and maximum sliding force remained below 5N.

It will be understood that the invention has been described by way of example only and modifications may be made whilst remaining within the scope and spirit of the invention.

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## CLAIMS

1. A pre-filled syringe, the syringe comprising a glass body, a stopper and a plunger, the body comprising an outlet at an outlet end and the stopper being arranged within the body such that a front surface of the stopper and the body define a variable volume chamber from which a fluid can be expelled though the outlet, the plunger comprising a plunger contact surface at a first end and a rod extending between the plunger contact surface and a rear portion, the plunger contact surface arranged to contact the stopper, such that the plunger can be used to force the stopper towards the outlet end of the body, reducing the volume of the variable volume chamber, characterised in that the fluid is an ophthalmic solution which comprises a VEGF-antagonist, wherein:

(a) the syringe has a nominal maximum fill volume of between about 0.5ml and about 1ml,

(b) the syringe is filled with a dosage volume of about 0.05ml of said VEGF antagonist solution,

(c) the syringe barrel comprises less than about 500μg silicone oil,

(d) the VEGF antagonist solution comprises no more than 2 particles ≥50μm in diameter per ml. and

(e) the VEGF antagonist is the non-antibody VEGF antagonist aflibercept at a concentration of 40mg/ml.

2. A pre-filled syringe according to claim 1, wherein the syringe barrel has an internal coating of about 1μg-about 500μg, about 3μg-about 200μg, about 5μg-about 100μg or about 10μg-about 50μg silicone oil.

3. A pre-filled syringe according to claim 1 or 2, wherein the syringe has a stopper break loose force of less than about 11N.

4. A pre-filled syringe according to any one of the previous claims, wherein the VEGF antagonist solution further comprises (i) no more than 5 particles ≥25μm in diameter per ml, (ii) no more than 50 particles ≥10μm in diameter per ml, or a combination of both (i) and (ii).

5. A blister pack comprising a pre-filled syringe according to any one of the previous claims, wherein the syringe has been sterilised using $H_2O_2$ to a Sterility Assurance Level of at least $10^{-6}$.

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**ABSTRACT**

The present invention relates to a device and in particular a syringe, more particularly to a small volume syringe such as a syringe suitable for ophthalmic injections.

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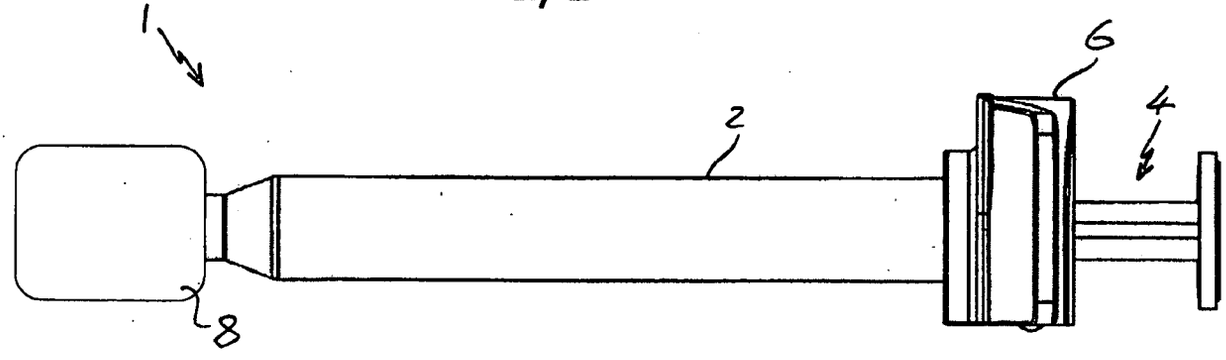


Fig 1

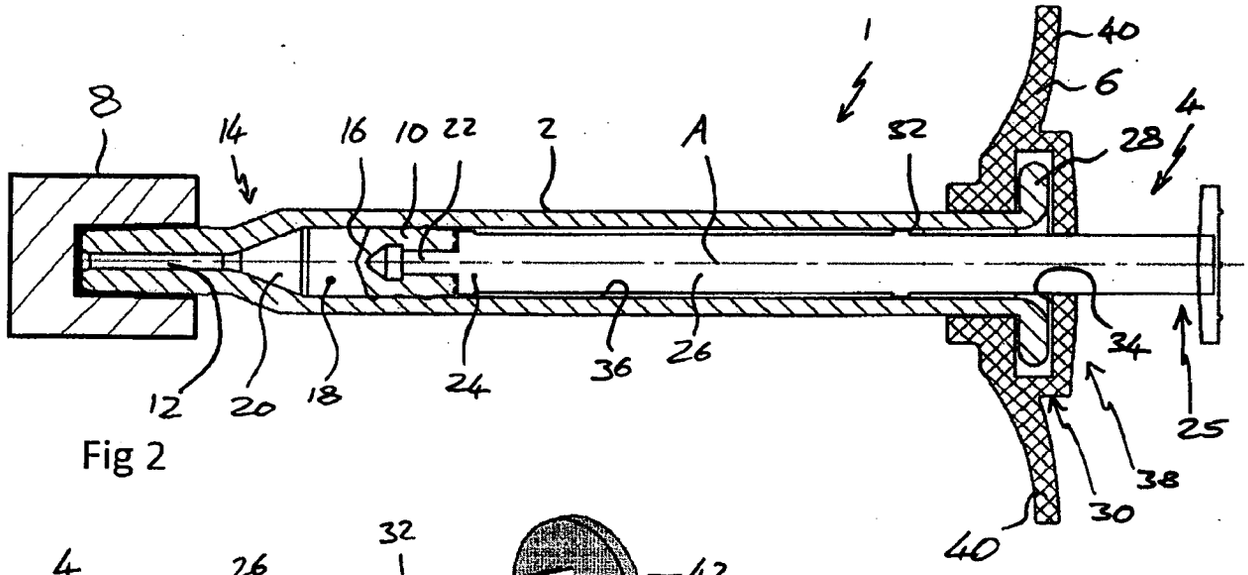


Fig 2

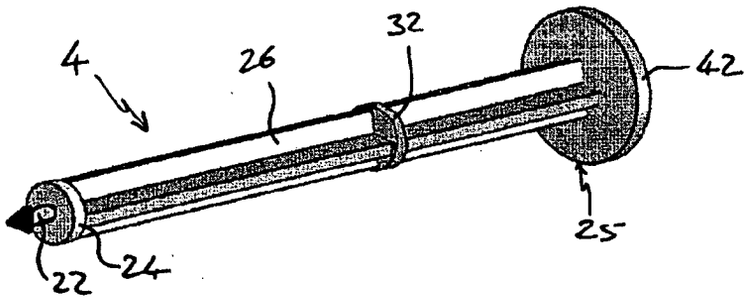


Fig 3

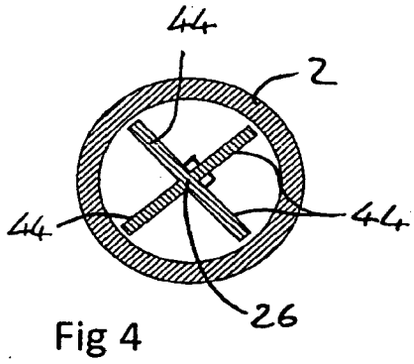


Fig 4

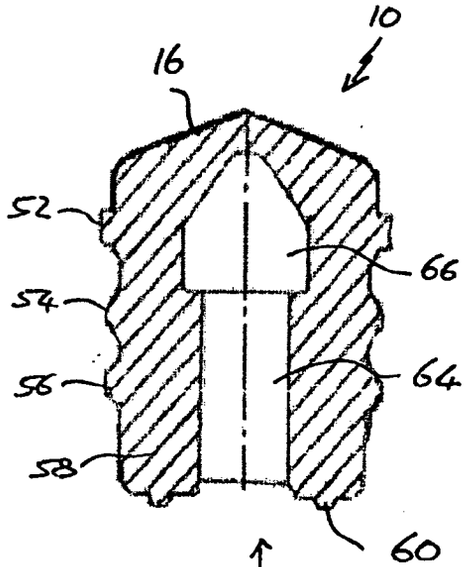


Fig 5

DocCode – SCORE

## SCORE Placeholder Sheet for IFW Content

Application Number: **13750352** Filing Date: **03/15/2013**

The presence of this form in the IFW record indicates that the following document is stored in the SCORE database

- Certified Copy of Foreign Application with Color Illustrations

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I, ALITA CLARK, PATENT AND PLANT BREEDERS RIGHTS ADMINISTRATION (PPBRA) hereby certify that annexed is a true copy of the Complete specification in connection with Innovation Patent No. 2013100070 for a patent by NOVARTIS AG as filed on 23 January 2013.

WITNESS my hand this
Nineteenth day of February 2013

A Clark

ALITA CLARK
PATENT AND PLANT BREEDERS
RIGHTS ADMINISTRATION (PPBRA)

COMMONWEALTH OF AUSTRALIA
AUSTRALIA
PATENT OFFICE

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# USE OF DEVICE

## TECHNICAL FIELD

The present invention relates to a syringe, particularly to a small volume syringe such as a syringe suitable for ophthalmic injections.

## BACKGROUND ART

Many medicaments are delivered to a patient in a syringe from which the user can dispense the medicament. If medicament is delivered to a patient in a syringe it is often to enable the patient, or a caregiver, to inject the medicament. It is important for patient safety and medicament integrity that the syringe and the contents of that syringe are sufficiently sterile to avoid infection, or other, risks for patients. Sterilisation can be achieved by terminal sterilisation in which the assembled product, typically already in its associated packaging, is sterilised using heat or a sterilising gas.

For small volume syringes, for example those for injections into the eye in which it is intended that about 0.1ml or less of liquid is to be injected the sterilisation can pose difficulties that are not necessarily associated with larger syringes. Changes in pressure, internal or external to the syringe, can cause parts of the syringe to move unpredictably, which may alter sealing characteristics and potentially compromise sterility. Incorrect handling of the syringe can also pose risks to product sterility.

Furthermore, certain therapeutics such as biologic molecules are particularly sensitive to sterilisation, be it cold gas sterilisation, thermal sterilisation, or irradiation. Thus, a careful balancing act is required to ensure that while a suitable level of sterilisation is carried out, the syringe remains suitably sealed, such that the therapeutic is not compromised. Of course, the syringe must also remain easy to use, in that the force required to depress the plunger to administer the medicament must not be too high.

There is therefore a need for a new syringe construct which provides a robust seal for its content, but which maintains ease of use.

## DISCLOSURE OF THE INVENTION

The present invention provides a pre-filled syringe, the syringe comprising a body, a stopper and a plunger, the body comprising an outlet at an outlet end and the stopper being arranged within the body such that a front surface of the stopper and the body define a variable volume chamber

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from which a fluid can be expelled though the outlet, the plunger comprising a plunger contact surface at a first end and a rod extending between the plunger contact surface and a rear portion, the plunger contact surface arranged to contact the stopper, such that the plunger can be used to force the stopper towards the outlet end of the body, reducing the volume of the variable volume chamber, characterised in that the fluid comprises an ophthalmic solution. In one embodiment, the ophthalmic solution comprises a VEGF-antagonist.

In one embodiment, the syringe is suitable for ophthalmic injections, more particularly intravitreal injections, and as such has a suitably small volume. The syringe may also be silicone oil free, or substantially silicone oil free, or may comprise a low level of silicone oil as lubricant. In one embodiment, despite the low silicone oil level, the stopper break loose and slide force is less than 20N.

For ophthalmic injections, it is particularly important for the ophthalmic solution to have particularly low particle content. In one embodiment, the syringe meets US Pharmacopeia standard 789 (USP789).

***Syringe***

The body of the syringe may be a substantially cylindrical shell, or may include a substantially cylindrical bore with a non circular outer shape. The outlet end of the body includes an outlet through which a fluid housed within the variable volume chamber can be expelled as the volume of said chamber is reduced. The outlet may comprise a projection from the outlet end through which extends a channel having a smaller diameter than that of the variable volume chamber. The outlet may be adapted, for example via a luer lock type connection, for connection to a needle or other accessory such as a sealing device which is able to seal the variable volume chamber, but can be operated, or removed, to unseal the variable volume chamber and allow connection of the syringe to another accessory, such as a needle. Such a connection may be made directly between the syringe and accessory, or via the sealing device. The body extends along a first axis from the outlet end to a rear end.

The body may be made from a plastic material (e.g. a cyclic olefin polymer) or from glass and may include indicia on a surface thereof to act as an injection guide. In one embodiment the body may comprise a priming mark. This allows the physician to align a pre-determined part of the stopper (such as the tip of the front surface or one of the circumferential ribs, discussed later) or plunger with the mark, thus expelling excess ophthalmic solution and any air bubbles from the

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syringe. The priming process ensures that an exact, pre-determined dosage is administered to the patient.

The stopper may be made from rubber, silicone or other suitable resiliently deformable material. The stopper may be substantially cylindrical and the stopper may include one or more circumferential ribs around an outer surface of the stopper, the stopper and ribs being dimensioned such that the ribs form a substantially fluid tight seal with an internal surface of the syringe body. The front surface of the stopper may be any suitable shape, for example substantially planar, substantially conical or of a domed shape. The rear surface of the stopper may include a substantially central recess. Such a central recess could be used to connect a plunger to the stopper using a snap fit feature or thread connection in a known manner. The stopper may be substantially rotationally symmetric about an axis through the stopper.

The plunger comprises a plunger contact surface and extending from that a rod extends from the plunger contact surface to a rear portion. The rear portion may include a user contact portion adapted to be contacted by a user during an injection event. The user contact portion may comprise a substantially disc shaped portion, the radius of the disc extending substantially perpendicular to the axis along which the rod extends. The user contact portion could be any suitable shape. The axis along which the rod extends may be the first axis, or may be substantially parallel with the first axis.

The syringe may include a backstop arranged at a rear portion of the body. The backstop may be removable from the syringe. If the syringe body includes terminal flanges at the end opposite the outlet end the backstop may be configured to substantially sandwich terminal flanges of the body as this prevent movement of the backstop in a direction parallel to the first axis.

The rod may comprise at least one rod shoulder directed away from the outlet end and the backstop may include a backstop shoulder directed towards the outlet end to cooperate with the rod shoulder to substantially prevent movement of the rod away from the outlet end when the backstop shoulder and rod shoulder are in contact. Restriction of the movement of the rod away from the outlet end can help to maintain sterility during terminal sterilisation operations, or other operations in which the pressure within the variable volume chamber or outside the chamber may change. During such operations any gas trapped within the variable volume chamber, or bubbles that may form in a liquid therein, may change in volume and thereby cause the stopper to move. Movement of the stopper away from the outlet could result in the breaching of a sterility zone created by the stopper. This is particularly important for low volume syringes

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where there are much lower tolerances in the component sizes and less flexibility in the stopper. The term sterility zone as used herein is used to refer to the area within the syringe that is sealed by the stopper from access from either end of the syringe. This may be the area between a seal of the stopper, for example a circumferential rib, closest to the outlet and a seal of the stopper, for example a circumferential rib, furthest from the outlet. The distance between these two seals defines the sterility zone of the stopper since the stopper is installed into the syringe barrel in a sterile environment.

To further assist in maintaining sterility during the operations noted above the stopper may comprise at a front circumferential rib and a rear circumferential rib and those ribs may be separated in a direction along the first axis by at least 3mm, by at least 3.5 mm, by at least 3.75mm or by 4mm or more. One or more additional ribs (for example 2, 3, 4 or 5 additional ribs, or between 1-10, 2-8, 3-6 or 4-5 additional ribs) may be arranged between the front and rear ribs. In one embodiment there are a total of three circumferential ribs.

A stopper with such an enhanced sterility zone can also provide protection for the injectable medicament during a terminal sterilisation process. More ribs on the stopper, or a greater distance between the front and rear ribs can reduce the potential exposure of the medicament to the sterilising agent. However, increasing the number of ribs can increase the friction between the stopper and syringe body, reducing ease of use. While this may be overcome by increasing the siliconisation of the syringe, such an increase in silicone oil levels is particularly undesirable for syringes for ophthalmic use.

The rod shoulder may be arranged within the external diameter of the rod, or may be arranged outside the external diameter of the rod. By providing a shoulder that extends beyond the external diameter of the rod, but still fits within the body, the shoulder can help to stabilise the movement of the rod within the body by reducing movement of the rod perpendicular to the first axis. The rod shoulder may comprise any suitable shoulder forming elements on the rod, but in one embodiment the rod shoulder comprises a substantially disc shaped portion on the rod.

In one embodiment of the syringe, when arranged with the plunger contact surface in contact with the stopper and the variable volume chamber is at its intended maximum volume there is a clearance of no more than about 2mm between the rod shoulder and backstop shoulder. In some embodiments there is a clearance of less than about 1.5 mm and in some less than about 1mm. This distance is selected to substantially limit or prevent excessive rearward (away from the outlet end) movement of the stopper.

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In one embodiment the variable volume chamber has an internal diameter greater than 5mm or 6mm, or less than 3mm or 4mm. The internal diameter may be between 3mm and 6mm, or between 4mm and 5mm.

In another embodiment the syringe is dimensioned so as to have a nominal maximum fill volume of between about 0.1ml and about 1.5ml. In certain embodiments the nominal maximum fill volume is between about 0.5ml and about 1ml. In certain embodiments the nominal maximum fill volume is about 0.5ml or about 1ml, or about 1.5ml.

The length of the body of the syringe may be less than 70mm, less than 60mm or less than 50mm. In one embodiment the length of the syringe body is between 45mm and 50mm.

In one embodiment, the syringe is filled with between about 0.01ml and about 1.5ml (for example between about 0.05ml and about 1ml, between about 0.1ml and about 0.5ml, between about 0.15ml and about 0.175ml) of a VEGF antagonist solution. In one embodiment, the syringe is filled with 0.165ml of a VEGF antagonist solution. Of course, typically a syringe is filled with more than the desired dose to be administered to the patient, to take into account wastage due to "dead space" within the syringe and needle. There may also be a certain amount of wastage when the syringe is primed by the physician, so that it is ready to inject the patient.

Thus, in one embodiment, the syringe is filled with a dosage volume (i.e. the volume of medicament intended for delivery to the patent) of between about 0.01ml and about 1.5ml (e.g. between about 0.05ml and about 1ml, between about 0.1ml and about 0.5ml) of a VEGF antagonist solution. In one embodiment, the dosage volume is between about 0.03ml and about 0.05ml. For example, for Lucentis, the dosage volume is 0.05ml or 0.03ml (0.5mg or 0.3mg) of a 10mg/ml injectable medicament solution; for Eylea, the dosage volume is 0.05ml of a 40mg/ml injectable medicament solution. Although unapproved for ophthalmic indications, bevacizumab is used off-label in such ophthalmic indications at a concentration of 25mg/ml; typically at a dosage volume of 0.05ml (1.25mg). In one embodiment, the extractable volume from the syringe (that is the amount of product obtainable from the syringe following filling, taking into account loss due to dead space in the syringe and needle) is about 0.09ml.

In one embodiment the length of the syringe body is between about 45mm and about 50mm, the internal diameter is between about 4mm and about 5mm, the fill volume is between about 0.12 and about 0.3ml and the dosage volume is between about 0.03ml and about 0.05ml.

As the syringe contains a medicament solution, the outlet may be reversibly sealed to maintain sterility of the medicament. This sealing may be achieved through the use of a sealing device as is known in the art. For example the OVS™ system which is available from Vetter Pharma International GmbH.

It is typical to siliconise the syringe in order to allow ease of use, i.e. to apply silicone oil to the inside of the barrel, which decreases the force required to move the stopper. However, for ophthalmic use, it is desirable to decrease the likelihood of silicone oil droplets being injected into the eye. With multiple injections, the amount of silicone droplets can build up in the eye, causing potential adverse effects, including "floaters" and an increase in intra-ocular pressure. Furthermore, silicone oil can cause proteins to aggregate. A typical 1ml syringe comprises 100-800µg silicone oil in the barrel, though a survey of manufacturers reported that 500-1000µg was typically used in pre-filled syringes (Badkar *et al.* 2011, AAPS PharmaSciTech, 12(2):564-572). Thus, in one embodiment, a syringe according to the invention comprises less than about 800µg (i.e. about less than about 500µg, less than about 300µg, less than about 200µg, less than about 100µg, less than about 75µg, less than about 50µg, less than about 25µg, less than about 15µg, less than about 10µg) silicone oil in the barrel. If the syringe comprises a low level of silicone oil, this may be more than about 1µg, more than about 3µg, more than about 5µg, more than about 7µg or more than about 10µg silicone oil in the barrel. Thus, in one embodiment, the syringe may comprise about 1µg-about 500µg, about 3µg-about 200µg, about 5µg-about 100µg or about 10µg-about 50µg silicone oil in the barrel. Methods for measuring the amount of silicone oil in such a syringe barrel are known in the art and include, for example, differential weighing methods and quantitation by infrared-spectroscopy of the oil diluted in a suitable solvent. Various types of silicone oil are available, but typically either DC360 (Dow Corning®; with a viscosity of 1000cP) or DC365 emulsion (Dow Corning®; DC360 oil with a viscosity of 350cP) are used for syringe siliconisation. In one embodiment, the pre-filled syringe of the invention comprises DC365 emulsion.

During testing it was surprisingly found that, for syringes having small dimensions, such as those discussed above, and particularly those described in conjunction with the Figures below, the break loose and sliding forces for the stopper within the syringe are substantially unaffected by reducing the siliconisation levels far below the current standard to the levels discussed here. This is in contrast to conventional thinking that would suggest that if you decrease the silicone oil level, the forces required would increase (see e.g. Schoenknecht, AAPS National Biotechnology Conference 2007 – Abstract no. NBC07-000488, which indicates that while 400µg silicone oil is

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acceptable, usability improves when increased to 800μg). Having too great a force required to move the stopper can cause problems during use for some users, for example accurate dose setting or smooth dose delivery may be made more difficult if significant strength is required to move, and/or keep in motion, the stopper. Smooth administration is particularly important in sensitive tissues such as the eye, where movement of the syringe during administration could cause local tissue damage. Break loose and slide forces for pre-filled syringes known in the art are typically in the region of less than 20N, but where the pre-filled syringes contain about 100μg-about 800μg silicone oil. In one embodiment the glide/slide force for the stopper within the pre-filled syringe is less than about 11N or less than 9N, less than 7N, less than 5N or between about 3N to 5N. In one embodiment, the break loose force is less than about 11N or less than 9N, less than 7N, less than 5N or between about 2N to 5N. Note that such measurements are for a filled syringe, rather than an empty syringe. The forces are typically measured at a stopper travelling speed of 190mm/min. In one embodiment, the forces are measured with a 30G x 0.5 inch needle attached to the syringe. In one embodiment, the syringe has a nominal maximal fill volume of between about 0.5ml and 1ml, contains less than about 100μg silicone oil and has a break loose force between about 2N to 5N.

In one embodiment the syringe barrel has an internal coating of silicone oil that has an average thickness of about 450nm or less (i.e. 400nm or less, 350nm or less, 300nm or less, 200nm or less, 100nm or less, 50nm or less, 20nm or less). Methods to measure the thickness of silicone oil in a syringe are known in the art and include the rap.ID Layer Explorer® Application, which can also be used to measure the mass of silicone oil inside a syringe barrel.

In one embodiment, the syringe is silicone oil free, or substantially silicone oil free. Such low silicone oil levels can be achieved by using uncoated syringe barrels and/or by avoiding the use of silicone oil as a lubricant for product contacting machine parts, or pumps in the syringe assembly and fill line. A further way to reduce silicone oil and inorganic silica levels in a pre-filled syringe is to avoid the use of silicone tubing in filling lines, for example between storage tanks and pumps.

The syringe according to the invention may also meet certain requirements for particulate content. In one embodiment, the ophthalmic solution comprises no more than 2 particles ≥50μm in diameter per ml. In one embodiment, the ophthalmic solution comprises no more than 5 particles ≥25μm in diameter per ml. In one embodiment, the ophthalmic solution comprises no more than 50 particles ≥10μm in diameter per ml. In one embodiment, the ophthalmic solution

comprises no more than 2 particles ≥50μm in diameter per ml, no more than 5 particles ≥25μm in diameter per ml and no more than 50 particles ≥10μm in diameter per ml. In one embodiment, a syringe according to the invention meets USP789 (United States Pharmacopoeia: Particulate Matter in Ophthalmic Solutions). In one embodiment the syringe has low levels of silicone oil sufficient for the syringe to meet USP789.

***VEGF Antagonists***

*Antibody VEGF antagonists*

VEGF is a well-characterised signal protein which stimulates angiogenesis. Two antibody VEGF antagonists have been approved for human use, namely ranibizumab (Lucentis®) and bevacizumab (Avastin®).

*Non-Antibody VEGF antagonists*

In one aspect of the invention, the non-antibody VEGF antagonist is an immunoadhesin. One such immuoadhesin is aflibercept (Eylea®), which has recently been approved for human use and is also known as VEGF-trap (Holash *et al.* (2002) *PNAS USA* 99:11393-98; Riely & Miller (2007) *Clin Cancer Res* 13:4623-7s). Aflibercept is the preferred non-antibody VEGF antagonist for use with the invention. Aflibercept is a recombinant human soluble VEGF receptor fusion protein consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1. It is a dimeric glycoprotein with a protein molecular weight of 97 kilodaltons (kDa) and contains glycosylation, constituting an additional 15% of the total molecular mass, resulting in a total molecular weight of 115 kDa. It is conveniently produced as a glycoprotein by expression in recombinant CHO K1 cells. Each monomer can have the following amino acid sequence (SEQ ID NO: 1):

SDTGRPFVEMYSEIPEIIHMTEGRELVIPCRVTSPNITVTLKKFPLDTLIPDGKRIIWDSRKGFIISNATY
KEIGLLTCEATVNGHLYKTNYLTHRQTNTIIDVVLSPSHGIELSVGEKLVLNCTARTELNVGIDFNWEYPS
SKHQHKKLVNRDLKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSGLMTKKNSTFVRVHEKDKTHTCPP
CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST
YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVK
GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL
SLSPG

and disulfide bridges can be formed between residues 30-79, 124-185, 246-306 and 352-410 within each monomer, and between residues 211-211 and 214-214 between the monomers.

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Another non-antibody VEGF antagonist immunoadhesin currently in pre-clinical development is a recombinant human soluble VEGF receptor fusion protein similar to VEGF-trap containing extracellular ligand-binding domains 3 and 4 from VEGFR2/KDR, and domain 2 from VEGFR1/Flt-1; these domains are fused to a human IgG Fc protein fragment (Li et al., 2011 *Molecular Vision* 17:797-803). This antagonist binds to isoforms VEGF-A, VEGF-B and VEGF-C. The molecule is prepared using two different production processes resulting in different glycosylation patterns on the final proteins. The two glycoforms are referred to as KH902 (conbercept) and KH906. The fusion protein can have the following amino acid sequence (SEQ ID NO:2):

MVSYWDTGVLLCALLSCLLLTGSSSGGRPFVEMYSEIPEIIHMTEGRELVIPCRVTSPNITVTLKKFPLDT
LIPDGKRIIWDSRKGFIISNATYKEIGLLTCEATVNGHLYKTNYLTHRQTNTIIDVVLSPSHGIELSVGEK
LVLNCTARTELNVGIDFNWEYPSSKHQHKKLVNRDLKTQSGSEMKKFLSTLTIDGVTRSDQGLYTCAASSG
LMTKKNSTFVRVHEKPFVAFGSGMESLVEATVGERVRLPAKYLGYPPPEIKWYKNGIPLESNHTIKAGHVL
TIMEVSERDTGNYTVILTNPISKEKQSHVVSLVVYVPPGPGDKTHTCPLCPAPELLGGPSVFLFPPKPKDT
LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC
KVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
ATPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

and, like VEGF-trap, can be present as a dimer. This fusion protein and related molecules are further characterized in EP1767546.

Other non-antibody VEGF antagonists include antibody mimetics (*e.g.* Affibody® molecules, affilins, affitins, anticalins, avimers, Kunitz domain peptides, and monobodies) with VEGF antagonist activity. This includes recombinant binding proteins comprising an ankyrin repeat domain that binds VEGF-A and prevents it from binding to VEGFR-2. One example for such a molecule is DARPin® MP0112. The ankyrin binding domain may have the following amino acid sequence (SEQ ID NO: 3):

GSDLGKKLLEAARAGQDDEVRILMANGADVNTADSTGWTPLHLAVPWGHLEIVEVLLKYGADVNAKDFQGW
TPLHLAAAIGHQEIVEVLLKNGADVNAQDKFGKTAFDISIDNGNEDLAEILQKAA

Recombinant binding proteins comprising an ankyrin repeat domain that binds VEGF-A and prevents it from binding to VEGFR-2 are described in more detail in WO2010/060748 and WO2011/135067.

Further specific antibody mimetics with VEGF antagonist activity are the 40 kD pegylated anticalin PRS-050 and the monobody angiocept (CT-322).

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The afore-mentioned non-antibody VEGF antagonist may be modified to further improve their pharmacokinetic properties or bioavailability. For example, a non-antibody VEGF antagonist may be chemically modified (e.g., pegylated) to extend its *in vivo* half-life. Alternatively or in addition, it may be modified by glycosylation or the addition of further glycosylation sites not present in the protein sequence of the natural protein from which the VEGF antagonist was derived.

Variants of the above-specified VEGF antagonists that have improved characteristics for the desired application may be produced by the addition or deletion of amino acids. Ordinarily, these amino acid sequence variants will have an amino acid sequence having at least 60% amino acid sequence identity with the amino acid sequences of SEQ ID NO: 1, SEQ ID NO: 2 or SEQ ID NO: 3, preferably at least 80%, more preferably at least 85%, more preferably at least 90%, and most preferably at least 95%, including for example, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, and 100%. Identity or homology with respect to this sequence is defined herein as the percentage of amino acid residues in the candidate sequence that are identical with SEQ ID NO: 1, SEQ ID NO: 2 or SEQ ID NO: 3, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity.

Sequence identity can be determined by standard methods that are commonly used to compare the similarity in position of the amino acids of two polypeptides. Using a computer program such as BLAST or FASTA, two polypeptides are aligned for optimal matching of their respective amino acids (either along the full length of one or both sequences or along a pre-determined portion of one or both sequences). The programs provide a default opening penalty and a default gap penalty, and a scoring matrix such as PAM 250 [a standard scoring matrix; see Dayhoff et al., in Atlas of Protein Sequence and Structure, vol. 5, supp. 3 (1978)] can be used in conjunction with the computer program. For example, the percent identity can then be calculated as: the total number of identical matches multiplied by 100 and then divided by the sum of the length of the longer sequence within the matched span and the number of gaps introduced into the longer sequences in order to align the two sequences.

Preferably, the non-antibody VEGF antagonist of the invention binds to VEGF via one or more protein domain(s) that are not derived from the antigen-binding domain of an antibody. The non-

antibody VEGF antagonist of the invention are preferably proteinaceous, but may include modifications that are non-proteinaceous (e.g., pegylation, glycosylation).

***Therapy***

The syringe of the invention may be used to treat an ocular disease, including but not limited to choroidal neovascularisation, age-related macular degeneration (both wet and dry forms), macular edema secondary to retinal vein occlusion (RVO) including both branch RVO (bRVO) and central RVO (cRVO), choroidal neovascularisation secondary to pathologic myopia (PM), diabetic macular edema (DME), diabetic retinopathy, and proliferative retinopathy.

Thus the invention provides a method of treating a patient suffering from of an ocular disease selected from choroidal neovascularisation, wet age-related macular degeneration, macular edema secondary to retinal vein occlusion (RVO) including both branch RVO (bRVO) and central RVO (cRVO), choroidal neovascularisation secondary to pathologic myopia (PM), diabetic macular edema (DME), diabetic retinopathy, and proliferative retinopathy, comprising the step of administering an ophthalmic solution to the patient using a pre-filled syringe of the invention. This method preferably further comprises an initial priming step in which the physician depresses the plunger of the pre-filled syringe to align the pre-determined part of the stopper with the priming mark.

In one embodiment, the invention provides a method of treating an ocular disease selected from choroidal neovascularisation, wet age-related macular degeneration, macular edema secondary to retinal vein occlusion (RVO) including both branch RVO (bRVO) and central RVO (cRVO), choroidal neovascularisation secondary to pathologic myopia (PM), diabetic macular edema (DME), diabetic retinopathy, and proliferative retinopathy, comprising administering a non-antibody VEGF antagonist with a pre-filled syringe of the invention, wherein the patient has previously received treatment with an antibody VEGF antagonist.

***Kits***

Also provided are kits comprising the pre-filled syringes of the invention. In one embodiment, such a kit comprises a pre-filled syringe of the invention in a blister pack. The blister pack may itself be sterile on the inside. In one embodiment, syringes according to the invention may be placed inside such blister packs prior to undergoing sterilisation, for example terminal sterilisation.

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Such a kit may further comprise a needle for administration of the VEGF antagonist. If the VEGF antagonist is to be administered intravitreally, it is typical to use a 30-gauge x ½ inch needle, though 31-gauge and 32-gauge needles may be used. For intravitreal administration, 33-gauge or 34-gauge needles could alternatively be used. Such kits may further comprise instructions for use. In one embodiment, the invention provides a carton containing a pre-filled syringe according to the invention contained within a blister pack, a needle and optionally instructions for administration.

***Sterilisation***

As noted above, a terminal sterilisation process may be used to sterilise the syringe and such a process may use a known process such as an ethylene oxide (EtO) or a hydrogen peroxide ($H_2O_2$) sterilisation process. Needles to be used with the syringe may be sterilised by the same method, as may kits according to the invention.

The package is exposed to the sterilising gas until the outside of the syringe is sterile. Following such a process, the outer surface of the syringe may remain sterile (whilst in its blister pack) for up to 6 months, 9 months, 12 months, 15 months, 18 months, 24 months or longer. Thus, in one embodiment, a syringe according to the invention (whilst in its blister pack) may have a shelf life of up to 6 months, 9 months, 12 months, 15 months, 18 months, 24 months or longer. In one embodiment, less than one syringe in a million has detectable microbial presence on the outside of the syringe after 18 months of storage. In one embodiment, the pre-filled syringe has been sterilised using EtO with a Sterility Assurance Level of at least $10^{-6}$. In one embodiment, the pre-filled syringe has been sterilised using hydrogen peroxide with a Sterility Assurance Level of at least $10^{-6}$. Of course, it is a requirement that significant amounts of the sterilising gas should not enter the variable volume chamber of the syringe. The term "significant amounts" as used herein refers to an amount of gas that would cause unacceptable modification of the ophthalmic solution within the variable volume chamber. In one embodiment, the sterilisation process causes ≤10% (preferably ≤5%, ≤3%, ≤1%) alkylation of the VEGF antagonist. In one embodiment, the pre-filled syringe has been sterilised using EtO, but the outer surface of the syringe has ≤1ppm, preferably ≤0.2ppm EtO residue. In one embodiment, the pre-filled syringe has been sterilised using hydrogen peroxide, but the outer surface of the syringe has ≤1ppm, preferably ≤0.2ppm hydrogen peroxide residue. In another embodiment, the pre-filled syringe has been sterilised using EtO, and the total EtO residue found on the outside of the syringe and inside of the blister pack is ≤0.1mg. In another embodiment, the pre-filled syringe has been sterilised using hydrogen

peroxide, and the total hydrogen peroxide residue found on the outside of the syringe and inside of the blister pack is ≤0.1mg.

***General***

The term "comprising" means "including" as well as "consisting" *e.g.* a composition "comprising" X may consist exclusively of X or may include something additional *e.g.* X + Y.

The term "about" in relation to a numerical value *x* means, for example, *x*±10%.

References to a percentage sequence identity between two amino acid sequences means that, when aligned, that percentage of amino acids are the same in comparing the two sequences. This alignment and the percent homology or sequence identity can be determined using software programs known in the art, for example those described in section 7.7.18 of *Current Protocols in Molecular Biology* (F.M. Ausubel *et al.*, eds., 1987) Supplement 30. A preferred alignment is determined by the Smith-Waterman homology search algorithm using an affine gap search with a gap open penalty of 12 and a gap extension penalty of 2, BLOSUM matrix of 62. The Smith-Waterman homology search algorithm is disclosed in Smith & Waterman (1981) *Adv. Appl. Math.* 2: 482-489

**BRIEF DESCRIPTION OF THE FIGURES**

Figure 1 shows a side view of a syringe

Figure 2 shows a cross section of a top down view of a syringe

Figure 3 shows a view of a plunger

Figure 4 shows a cross section though a plunger

Figure 5 shows a stopper

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## MODES FOR CARRYING OUT THE INVENTION

The invention will now be further described, by way of example only, with reference to the drawings.

Figure 1 shows a view from a side of a syringe 1 comprising a body 2, plunger 4, backstop 6 and a sealing device 8.

Figure 2 shows a cross section through the syringe 1 of Figure 1 from above. The syringe 1 is suitable for use in an ophthalmic injection. The syringe 1 comprises a body 2, a stopper 10 and a plunger 4. The syringe 1 extends along a first axis A. The body 2 comprises an outlet 12 at an outlet end 14 and the stopper 10 is arranged within the body 2 such that a front surface 16 of the stopper 10 and the body 2 define a variable volume chamber 18. The variable volume chamber 18 contains an injectable medicament 20 comprising an ophthalmic solution comprising a VEGF antagonist such as ranibizumab. The injectable fluid 20 can be expelled though the outlet 12 by movement of the stopper 10 towards the outlet end 14 thereby reducing the volume of the variable volume chamber 18. The plunger 4 comprises a plunger contact surface 22 at a first end 24 and a rod 26 extending between the plunger contact surface 22 and a rear portion 25. The plunger contact surface 22 is arranged to contact the stopper 10, such that the plunger 4 can be used to move the stopper 10 towards the outlet end 14 of the body 2. Such movement reduces the volume of the variable volume chamber 18 and causes fluid therein to be expelled though the outlet.

The backstop 6 is attached to the body 2 by coupling to a terminal flange 28 of the body 2. The backstop 6 includes sandwich portion 30 which is adapted to substantially sandwich at least some of the terminal flange 28 of the body 2. The backstop 6 is adapted to be coupled to the body 2 from the side by leaving one side of the backstop 6 open so that the backstop 6 can be fitted to the syringe 2.

The body 2 defines a substantially cylindrical bore 36 which has a bore radius. The rod 26 comprises a rod shoulder 32 directed away from the outlet end 14. The rod shoulder 32 extends from to a rod shoulder radius from the first axis A which is such that it is slightly less than the bore radius so that the shoulder fits within the bore 36. The backstop 6 includes a backstop shoulder 34 directed towards the outlet end 14. The shoulders 32, 34 are configured to cooperate to substantially prevent movement of the rod 26 away from the outlet end 14 when the backstop shoulder 34 and rod shoulder 32 are in contact. The backstop shoulder 34 extends from outside the bore radius to a radius less than the rod shoulder radius so that the rod shoulder 32 cannot pass the

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backstop shoulder 34 by moving along the first axis A. In this case the rod shoulder 32 is substantially disc, or ring, shaped and the backstop shoulder 34 includes an arc around a rear end 38 of the body 2.

The backstop 6 also includes two finger projections 40 which extend in opposite directions away from the body 2 substantially perpendicular to the first axis A to facilitate manual handling of the syringe 1 during use.

In this example the syringe comprises a 0.5ml body 2 filled with between about 0.1 and 0.3 ml of an injectable medicament 20 comprising a 10mg/ml injectable solution comprising ranibizumab. The syringe body 2 has an internal diameter of about between about 4.5mm and 4.8mm, a length of between about 45mm and 50mm.

The plunger 4 and stopper 10 will be described in more detail with reference to later figures.

Figure 3 shows a perspective view of the plunger 4 of Figure 1 showing the plunger contact surface 22 at the first end 24 of the plunger 4. The rod 26 extends from the first end 24 to the rear portion 25. The rear portion 25 includes a disc shaped flange 42 to facilitate user handling of the device. The flange 42 provides a larger surface area for contact by the user than a bare end of the rod 26.

Figure 4 shows a cross section though a syringe body 2 and rod 26. The rod 26 includes four longitudinal ribs 44 and the angle between the ribs is 90°.

Figure 5 shows a detailed view of a stopper 10 showing a conical shaped front surface 16 and three circumferential ribs 52,54,56 around a substantially cylindrical body 58. The axial gap between the first rib 52 and the last rib 56 is about 3mm. The rear surface 60 of the stopper 10 includes a substantially central recess 62. The central recess 62 includes an initial bore 64 having a first diameter. The initial bore 64 leading from the rear surface 60 into the stopper 10 to an inner recess 66 having a second diameter, the second diameter being larger than the first diameter.

***Stopper movement forces***

0.5ml syringes siliconised with <100µg silicone oil, filled with Lucentis, comprising one of two different stopper designs were tested for maximal and average break out and slide force. Prior to testing, 30G x 0.5" needles were attached to the syringes. The testing was carried out at a stopper speed of 190mm/min over a travel length of 10.9mm. Stopper design 2 had a 45% increase in the distance between the front circumferential rib and rear circumferential rib.

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| | | Stopper design 1 | | | Stopper design 2 | |
|---|---|---|---|---|---|---|
| | | Batch A | Batch B | Batch C | Batch D | Batch E |
| Break loose force of syringes | Average of 10 syringes | 2.2N | 2.3N | 1.9N | 2.1N | 2.5N |
| | Max individual value | 2.5N | 2.5N | 2.3N | 2.6N | 2.7N |
| Sliding force | Average of 10 syringes | 3.1N | 3.2N | 3.1N | 4.1N | 4.6N |
| | Max individual value | 3.5N | 3.5N | 3.6N | 4.7N | 4.8N |

For both stopper designs, average and maximum break out force remained below 3N. For both stopper designs, average and maximum sliding force remained below 5N.

It will be understood that the invention has been described by way of example only and modifications may be made whilst remaining within the scope and spirit of the invention.

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## CLAIMS

1. Use of a pre-filled syringe in the treatment of wet age-related macular degeneration, wherein the syringe comprises a glass body, a stopper and a plunger, the body comprising an outlet at an outlet end and the stopper being arranged within the body such that a front surface of the stopper and the body define a variable volume chamber from which a fluid can be expelled though the outlet, the plunger comprising a plunger contact surface at a first end and a rod extending between the plunger contact surface and a rear portion, the plunger contact surface arranged to contact the stopper, such that the plunger can be used to force the stopper towards the outlet end of the body, reducing the volume of the variable volume chamber, characterised in that the fluid is an ophthalmic solution which comprises a VEGF-antagonist, wherein:

(a) the syringe has a nominal maximum fill volume of between about 0.5ml and about 1ml,

(b) the syringe is filled with a dosage volume of about 0.05ml of said VEGF antagonist solution,

(c) the syringe barrel comprises less than about 500μg silicone oil,

(d) the VEGF antagonist solution comprises no more than 2 particles ≥50μm in diameter per ml, and

(e) the VEGF antagonist is the non-antibody VEGF antagonist aflibercept at a concentration of 40mg/ml.

2. A method of treating a patient suffering from wet age-related macular degeneration, comprising the step of administering an ophthalmic solution to the patient using a pre-filled syringe as defined in claim 1.

3. The method of claim 2, further comprising an initial priming step in which a user depresses the plunger of the pre-filled syringe to align the pre-determined part of the stopper with a priming mark.

4. A method according to claim 3, wherein the patient has previously received treatment with an antibody VEGF antagonist.

5. The use according to claim 1, or method according to any one of claims 2 to 4, wherein the VEGF antagonist solution further comprises (i) no more than 5 particles ≥25μm in diameter per ml, (ii) no more than 50 particles ≥10μm in diameter per ml; or a combination of both (i) and (ii).

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## ABSTRACT

The present invention relates to a device and in particular syringe, more particularly to a small volume syringe such as a syringe suitable for ophthalmic injections. The present invention also relates to uses of the device and methods.

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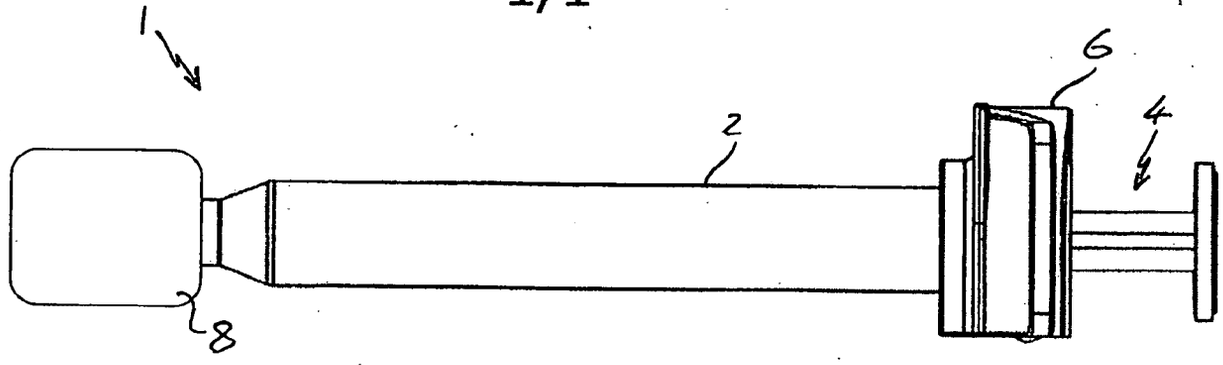


Fig 1

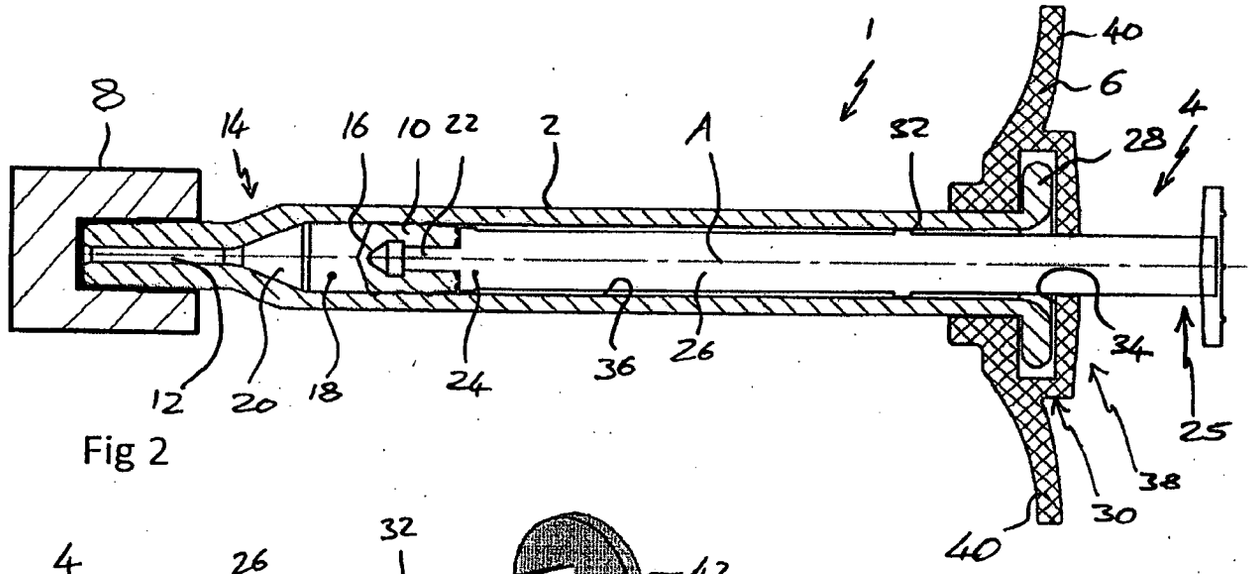


Fig 2

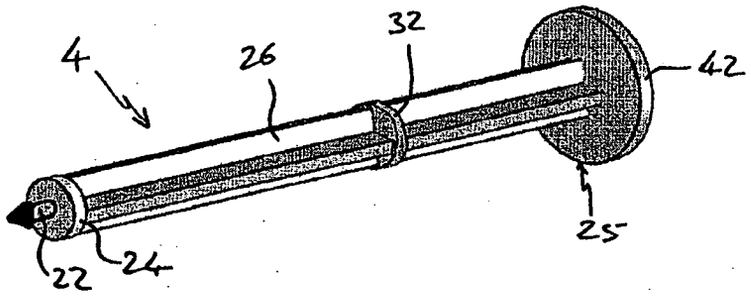


Fig 3

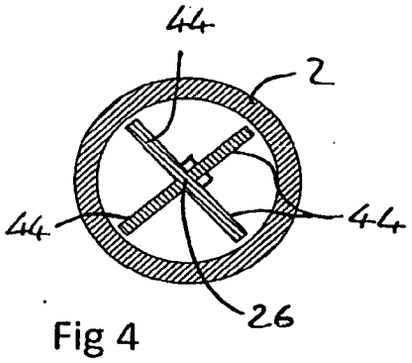


Fig 4

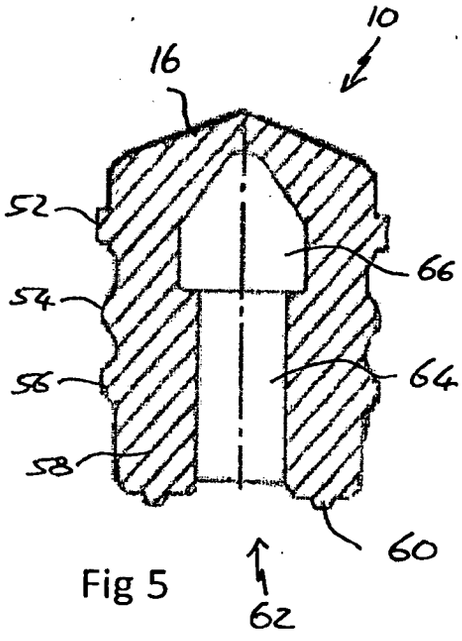


Fig 5

DocCode – SCORE

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CASE PAT055157-US-NP

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IN RE APPLICATION OF
Sigg, Juergen et al.
APPLICATION NO: 13/750352
FILED: January 25, 2013
FOR: SYRINGE

Art Unit: 3763
Examiner:

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

CLAIM OF PRIORITY UNDER 35 USC §119

Sir:

Applicants in the above-identified application hereby claim priority under the International Convention of the following:

| Country | Case | Number | Date |
|---|---|---|---|
| European Procedure | PAT055157-EP-EPA | 12174860.2 | 03 Jul 2012 |
| European Procedure | PAT055157-EP-EPA02 | 12189649.2 | 23 Oct 2012 |
| Germany | PAT055157-DE-UM | 202012011016.0 | 16 Nov 2012 |
| Australia | PAT055157-AU-STP | 2012101677 | 16 Nov 2012 |
| Australia | PAT055157-AU-STP02 | 2012101678 | 16 Nov 2012 |
| Germany | PAT055157-DE-UM02 | 202012011260.0 | 23 Nov 2012 |
| Germany | PAT055157-DE-UM03 | 202012011259.7 | 23 Nov 2012 |
| European Procedure | PAT055157-EP-EPA03 | 12195360.8 | 03 Dec 2012 |
| Germany | PAT055157-DE-UM04 | 202013000688.9 | 23 Jan 2013 |
| Australia | PAT055157-AU-STP03 | 2013100071 | 23 Jan 2013 |
| Australia | PAT055157-AU-STP04 | 2013100070 | 23 Jan 2013 |

These applications are acknowledged in the Application Data Sheet of the instant case.

The certified copy of said applications are submitted herewith.

/ Andrew Holmes /

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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE


Substitute for form 1449/PTO

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

*(Use as many sheets as necessary)*

| Sheet | 1 | of | 1 |
|---|---|---|---|

| Complete if Known | |
|---|---|
| Application Number | 13/750352 |
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| First Named Inventor | Sigg, Juergen et al. |
| Art unit | 3763 |
| Examiner Name | |
| Attorney Docket Number | PAT055157-US-NP |

**U.S. PATENT DOCUMENTS**

| Examiner Initials* | Cite No.[1] | Document Number<br>Number-Kind Code[2] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
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| | | US- | | | |
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**FOREIGN PATENT DOCUMENTS**

| Examiner Initials* | Cite No.[1] | Foreign Patent Document<br>Country Code[3] Number[4] Kind Code[5] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear | T[6] |
|---|---|---|---|---|---|---|
| | | WO 2011/123722 A1 | 10-06-2011 | OCUJECT, LLC | | ☐ |
| | | WO 2012/149040 A2 | 11-01-2012 | WONG, VERNON, G. | | ☐ |
| | | WO 2007/149334 A2 | 12-27-2007 | REGENERON PHARMACEUTICALS,INC | | ☐ |
| | | WO 2012/134528 A1 | 10-04-2012 | OCUJECT, LLC | | ☐ |
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(54) **Title**: DEVICE AND METHOD FOR INTRAOCULAR DRUG DELIVERY

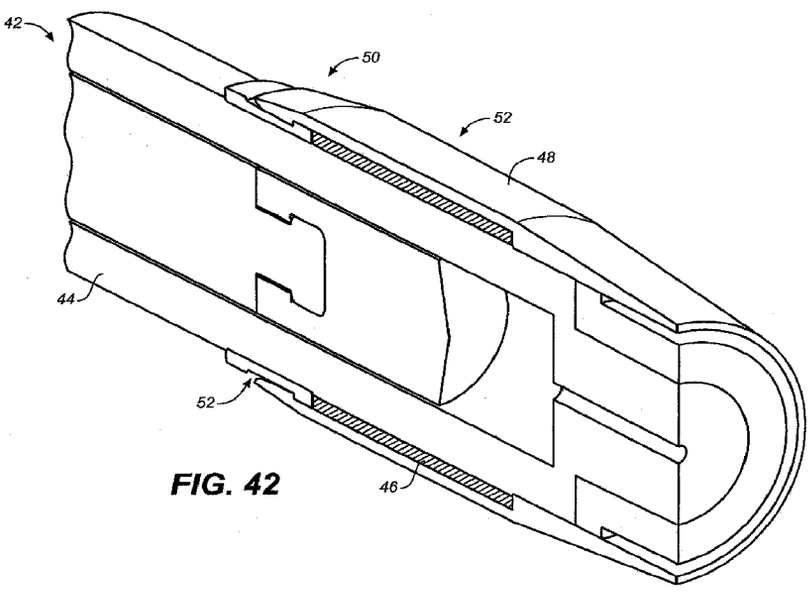



FIG. 42

(57) **Abstract**: Devices for delivering pharmaceutical formulations into the eye are described. The devices may be integrated to include features that allow safe and atraumatic manipulation of the devices with one hand. For example, accurate placement, including proper angulation, of the device on the eye and injection of a pharmaceutical formulation into the eye can be performed using one hand. The devices may also include improved safety features. For example, the devices may include an actuation mechanism that controls the rate and depth of injection into the eye. Some devices include a dynamic resistance component capable of adjusting the amount of pressure applied to the eye surface. Related methods and systems comprising the devices are also described.

WO 2011/123722 A1

# DEVICE AND METHOD FOR INTRAOCULAR DRUG DELIVERY

## CROSS-REFERENCE TO RELATED APPLICATIONS

**[0001]** This application claims priority to U.S. Provisional Application Serial No. 61/341,582 filed on March 31, 2010, U.S. Provisional Application Serial No. 61/384,636 filed on September 20, 2010, and U.S. Provisional Application Serial No. 61/422,220 filed on December 13, 2010, each of which is hereby incorporated by reference in its entirety.

## FIELD

**[0002]** Described here are devices that are configured to safely and accurately deliver pharmaceutical formulations into the eye. Specifically, the devices may integrate various features that allow easy manipulation of the devices, and which may be beneficial for positioning of the devices on the ocular surface and for injecting pharmaceutical formulations atraumatically within the eye. Systems and methods for intraocularly delivering the pharmaceutical formulations using the devices are also described.

## BACKGROUND

**[0003]** The eye is a complex organ comprised of many parts that enable the process of sight. Vision quality depends on the condition of each individual part and the ability of these parts to work together. For example, vision may be affected by conditions that affect the lens (e.g., cataracts), retina (e.g., CMV retinitis), or the macula (e.g., macular degeneration). Topical and systemic drug formulations have been developed to treat these and other ocular conditions, but each has its drawbacks. For example, topical therapies that are applied on the surface of the eye typically possess short residence times due to tear flow that washes them out of the eye. Furthermore, delivery of drugs into the eye is limited due to the natural barrier presented by the cornea and sclera, and additional structures if the intended target resides within the posterior chamber. With respect to systemic treatments, high doses of drug are often required in order to obtain therapeutic levels within the eye, which increases the risk of adverse side-effects.

**[0004]** Alternatively, intravitreal injections have been performed to locally deliver pharmaceutical formulations into the eye. The use of intravitreal injections has become more common due to the increased availability of anti-vascular endothelial growth factor agents for

the treatment of acute macular degeneration (AMD). Agents approved by the FDA for intravitreal injection to treat AMD include ranibizumab (Lucentis®: Genetech, South San Francisco, CA) and pegaptanib sodium (Macugen®: Eyetech Pharmaceuticals, New York, NY). In addition, intravitreal bevacizumab (Avastin®: Genentech, South San Francisco, CA) has been widely used in an off-label application to treat choroidal neovascularization. Increased interest in developing new drugs for delivery directly into the vitreous for the treatment of macular edema, retinal vein occlusion, and vitreous hemorrhage also exists.

**[0005]** Currently, commercially available intravitreal injection devices lack many features that are useful in exposing the site of injection, stabilizing the device against the sclera, and/or controlling the angle and depth of injection. Many of the devices described in the patent literature, e.g., WO 2008/084064 and U.S. 2007/0005016, are also part of multi-component systems that are generally time consuming to set up and use. The increased procedure time associated with these devices may in turn increase the risk of complications. Further, having to manipulate many components by itself may increase the risk of complications due to user error. A serious complication of intraocular injection is intraocular infection, termed endophthalmitis that occurs due to the introduction of pathogenic organisms such as bacteria from the ocular surface into the intraocular environment, or trauma to the ocular surface tissues such as corneal or conjunctival abrasion.

**[0006]** Accordingly, new devices for performing intravitreal injections would be desirable. Ergonomic devices that simplify the injection procedure and reduce the risk of complications would be useful. Devices that accurately and atraumatically inject drugs, e.g., liquid, semisolid, or suspension-based drugs, into the eye would also be useful.

## SUMMARY

**[0007]** Described here are devices, methods, and systems for delivering pharmaceutical formulations into the eye. The devices may be integrated. By "integrated" it is meant that various features that may be beneficial in delivering the pharmaceutical formulations into the eye, e.g., in a safe, sterile, and accurate manner, are combined into a single device. For example, features that may aid appropriate placement on the desired eye surface site, help position the device so that the intraocular space is accessed at the proper angle, help to keep the device tip stable without moving or sliding on the ocular surface once it has been positioned during the entire drug injection, adjust or control intraocular pressure, and/or help

to minimize trauma, e.g., from the force of drug injection or contact or penetration of the eye wall itself, may be integrated into a single device. More specifically, the integrated devices may be used in minimizing trauma due to direct contact with the target tissue or indirectly through force transmission through another tissue or tissues such as the eye wall or vitreous gel, as well as minimizing trauma to the cornea, conjunctiva, episclera, sclera, and intraocular structures including, but not limited to, the retina, the choroid, the ciliary body, and the lens, as well as the blood vessels and nerves associated with these structures. Features that may be beneficial in reducing the risk of intraocular infectious inflammation such as endophthalmitis and those that may reduce pain may also be included. It should be understood that the pharmaceutical formulations may be delivered to any suitable target location within the eye, e.g., the anterior chamber or posterior chamber. Furthermore, the pharmaceutical formulations may include any suitable active agent and may take any suitable form. For example, the pharmaceutical formulations may be a solid, semi-solid, liquid, etc. The pharmaceutical formulations may also be adapted for any suitable type of release. For example, they may be adapted to release an active agent in an immediate release, controlled release, delayed release, sustained release, or bolus release fashion.

**[0008]** In general, the devices described here include a housing sized and shaped for manipulation with one hand. The housing typically has a proximal end and a distal end, and an ocular contact surface at the housing distal end. A conduit in its pre-deployed state will usually reside within the housing. The conduit will be at least partially within the housing in its deployed state. In some instances, the conduit is slidably attached to the housing. The conduit will generally have a proximal end, a distal end, and a lumen extending therethrough. An actuation mechanism may be contained within the housing that is operably connected to the conduit and a reservoir for holding an active agent. A trigger may also be coupled to the housing and configured to activate the actuation mechanism. In one variation, a trigger is located on the side of the device housing in proximity to the device tip at the ocular contact surface (the distance between the trigger and device tip ranging between 5 mm to 50 mm, between 10 mm to 25 mm, or between 15 mm to 20 mm), so that the trigger can be easily activated by a fingertip while the device is positioned over the desired ocular surface site with the fingers of the same hand. In another variation, a trigger is located on the side of the device housing at 90 degrees to a measuring component, so that when the device tip is placed on the eye surface perpendicular to the limbus, the trigger can be activated with the tip of the second or third finger of the same hand that positions the device on the ocular surface. In one

variation, a measuring component is attached to the ocular contact surface. In some variations, a drug loading mechanism is also included.

**[0009]** The actuation mechanism may be manual, automated, or partially automated. In one variation, the actuation mechanism is a spring-loaded actuation mechanism. Here the mechanism may include either a single spring or two springs. In another variation, the actuation mechanism is a pneumatic actuation mechanism.

**[0010]** The application of pressure to the surface of the eye may be accomplished and further refined by including a dynamic resistance component to the injection device. The dynamic resistance component may include a slidable element coupled to the housing. In some variations, the slidable element comprises a dynamic sleeve configured to adjust the amount of pressure applied to the eye surface. In other variations, the dynamic resistance component is configured as an ocular wall tension control mechanism.

**[0011]** In use, the devices deliver drug into the intraocular space by positioning an ocular contact surface of the integrated device on the surface of an eye, where the device further comprises a reservoir for holding an active agent and an actuation mechanism, and applying pressure against the surface of the eye at a target injection site using the ocular contact surface, and then delivering an active agent from the reservoir into the eye by activating the actuation mechanism. The steps of positioning, applying, and delivering are completed with one hand. In some instances, a topical anesthetic is applied to the surface of the eye before placement of the device on the eye. An antiseptic may also be applied to the surface of the eye before placement of the device on the eye.

**[0012]** The application of pressure against the surface of the eye using the ocular contact surface may also generate an intraocular pressure ranging between 15 mm Hg to 120 mm Hg, between 20 mm Hg to 90 mm Hg, or between 25 mm Hg to 60 mm Hg. As further described below, the generation of intraocular pressure before deployment of the dispensing member (conduit) may reduce scleral pliability, which in turn may facilitate the penetration of the conduit through the sclera, decrease unpleasant sensation associated with the conduit penetration through the eye wall during an injection procedure and/or prevent backlash of the device.

**[0013]** The drug delivery devices, components thereof, and/or various active agents may be provided in systems or kits as separately packaged components. The systems or kits may

include one or more devices as well as one or more active agents. The devices may be preloaded or configured for manual drug loading. When a plurality of active agents is included, the same or different active agents may be used. The same or different doses of the active agent may be used as well. The systems or kits will generally include instructions for use. They may also include anesthetic agents and/or antiseptic agents.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0014]** FIGS. 1A-1B depict front views of exemplary ocular contact surfaces.

**[0015]** FIGS. 2A-2C show side views of additional exemplary ocular contact surfaces that include measuring components.

**[0016]** FIGS. 3A1-3A3 and FIGS. 3B1-3B3 show side views of other exemplary ocular contact surfaces.

**[0017]** FIGS. 4A and FIGS. 4B1-4B2 depict perspective and front views of an exemplary flanged ocular contact surface.

**[0018]** FIGS. 5A1-5A2 and FIGS. 5B1-5B2 depict side and perspective views of exemplary flat and convex ocular contact surfaces.

**[0019]** FIGS. 6A1-6A2 and FIGS. 6B1-6B2 show side and front views of exemplary soft or semi-solid ocular contact surfaces.

**[0020]** FIGS. 7A1-7A2, FIGS. 7B1-7B2, FIGS. 7C1-7C2, and FIGS. 7D-7E show additional exemplary ocular contact surfaces, including ocular contact surfaces having a high-traction interface.

**[0021]** FIG. 8 illustrates how an exemplary measuring component works to retract the eyelid and measure a certain distance from the limbus.

**[0022]** FIGS. 9A-9C show exemplary arrangements of measuring components around an ocular contact surface.

**[0023]** FIGS. 10A-10C depict other exemplary measuring components and how they work to measure a certain distance from the limbus.

**[0024]** FIGS. 11A-11D show further exemplary measuring components.

**[0025]** FIG. 12 shows an exemplary device that includes a marking tip member.

**[0026]** FIG. 13 illustrates how marks made on the surface of the eye by an exemplary marking tip member can be used to position the device at a target injection site.

**[0027]** FIGS. 14A-14C show perspective views of exemplary sharp conduits.

**[0028]** FIGS. 15A1-15A2 show side views of exemplary bevel angles.

**[0029]** FIGS. 16A-16D depict cross-sectional views of exemplary conduit geometries.

**[0030]** FIG. 17 depicts a cross-sectional view of additional exemplary conduit geometries.

**[0031]** FIGS. 18A-18C show side and cross-sectional views (taken along line A—A) of an exemplary flattened conduit.

**[0032]** FIG. 19 shows an exemplary mechanism for controlling exposure of the conduit.

**[0033]** FIG. 20 provides another exemplary conduit exposure control mechanism.

**[0034]** FIG. 21 shows an exemplary device having a front cover and back cover.

**[0035]** FIG. 22 illustrates how the device may be filled with a pharmaceutical formulation using an exemplary drug loading member.

**[0036]** FIGS. 23A-23C depict other examples of drug loading members.

**[0037]** FIGS. 24A-24D show an exemplary fenestrated drug loading member.

**[0038]** FIGS. 25A-25B show an exemplary fenestrated drug loading member interfaced with a drug source.

**[0039]** FIGS. 26A-26C depicts a side, cross-sectional view of an exemplary two-spring actuation mechanism.

**[0040]** FIG. 27 is a side, cross-sectional view of another exemplary two-spring actuation mechanism.

**[0041]** FIG. 28 depicts a perspective view of a device including a further example of a two-spring actuation mechanism in its pre-activated state.

**[0042]** FIG. 29 is a cross-sectional view of the device and two-spring actuation mechanism shown in FIG. 28.

**[0043]** FIG. 30 is a cross-sectional view of the device shown in FIG. 28 after the two-spring actuation mechanism has been activated.

**[0044]** FIGS. 31A-31C illustrate how the trigger in FIG. 28 actuates the first spring of the two-spring actuation mechanism to deploy the conduit.

**[0045]** FIGS. 32A-32C are expanded views that illustrate how release of the locking pins in FIG. 28 work to activate the second spring of the two-spring actuation mechanism.

**[0046]** FIGS. 33A-33B depict the device of FIG. 28 with an exemplary loading port.

**[0047]** FIG. 34 is a perspective view of an exemplary device with a pneumatic actuation mechanism.

**[0048]** FIGS. 35A-35B provide cross-sectional views of the device shown in FIG. 34. FIG. 35A show the pneumatic actuation mechanism in a pre-activated state. FIG. 35B shows the pneumatic actuation mechanism after deployment of the conduit.

**[0049]** FIG. 36 is a cross-sectional view of an exemplary device including a single spring actuation mechanism.

**[0050]** FIG. 37 is a cross-sectional view of the device shown in FIG. 36 that showing the single spring actuation mechanism after deployment of the conduit.

**[0051]** FIG. 38 is a side, cross-sectional view of an exemplary drug-loading piston.

**[0052]** FIGS. 39A-39I depict various views of exemplary device tips.

**[0053]** FIG. 40 shows an exemplary device with a sliding cap.

**[0054]** FIGS. 41A-41B provide cross-sectional views of another exemplary device having a two-spring actuation mechanism.

**[0055]** FIG. 42 depicts an enlarged sectional view an exemplary dynamic sleeve.

**[0056]** FIGS. 43A-43D illustrate an exemplary method of advancement of a dispensing member and drug injection.

**[0057]** FIGS. 44A-44D depict exemplary positional indicator components.

**[0058]** FIGS. 45A-45J show various aspects of exemplary fine sleeve mobility control components.

**[0059]** FIG. 46 is a graphic depiction of the amount of resistance force generated by a dynamic sleeve according to one variation.

## DETAILED DESCRIPTION

**[0060]** Described here are hand-held devices, methods, and systems for delivering, e.g., by injection, pharmaceutical formulations into the eye. The devices may integrate (combine) various features that may be beneficial in delivering the pharmaceutical formulations into the eye, e.g., in a safe, sterile, and accurate manner, into a single device. Thus, features that may aid appropriate placement on the eye, help positioning so that the intraocular space is accessed at the proper angle, adjust or control intraocular pressure, and/or help to minimize trauma to the sclera and intraocular structures, e.g., from the force of injection or penetration of the sclera itself, may be integrated into a single device. The devices, in whole or in part, may be configured to be disposable.

### I. DEVICES

**[0061]** In general, the integrated devices described here include a housing sized and shaped for manipulation with one hand. The housing typically has a proximal end and a distal end, and an ocular contact surface at the housing distal end. A conduit tin its pre-deployed state may reside within the housing. The conduit will be at least partially within the housing in its deployed state. In some variations, the conduit is slidably attached to the housing. Additionally, the conduit will generally have a proximal end, a distal end, and a lumen extending therethrough. An actuation mechanism may be contained within the housing that is operably connected to the conduit and a reservoir for holding an active agent.

**[0062]** The devices or portions thereof may be formed from any suitable biocompatible material or combination of biocompatible materials. For example, one or more biocompatible polymers may be used to make, e.g., the device housing, ocular contact

surface, measuring component, etc. Exemplary biocompatible and non-biodegradable materials include without limitation, methylmethacrylate (MMA), polymethylmethacrylate (PMMA), polyethylmethacrylate (PEM), and other acrylic-based polymers; polyolefins such as polypropylene and polyethylene; vinyl acetates; polyvinylchlorides; polyurethanes; polyvinylpyrollidones; 2-pyrrolidones; polyacrylonitrile butadiene; polycarbonates; polyamides; fluoropolymers such as polytetrafluoroethylene (e.g., TEFLON™ polymer); polystyrenes; styrene acrylonitriles; cellulose acetate; acrylonitrile butadiene styrene; polymethylpentene; polysulfones; polyesters; polyimides; natural rubber; polyisobutylene rubber; polymethylstyrene; silicone; and copolymers and blends thereof.

**[0063]** In some variations, the device or a portion of the device such as the drug reservoir, plunger, housing, ocular contact surface, or measuring component, is made of a material that includes a cyclic olefin series resin. Exemplary cyclic olefin resins include without limitation, commercially available products such as Zeonex® cyclo olefin polymer (ZEON Corporation, Tokyo, Japan) or Crystal Zenith® olefinic polymer (Daikyo Seiko, Ltd., Tokyo, Japan) and APEL™ cyclo olefin copolymer (COC) (Mitsui Chemicals, Inc., Tokyo, Japan), a cyclic olefin ethylene copolymer, a polyethylene terephthalate series resin, a polystyrene resin, a polybutylene terephthalate resin, and combinations thereof. In one variation, it may be beneficial to use a cyclic olefin series resin and a cyclic olefin ethylene copolymer that have high transparency, high heat resistance, and minimal to no chemical interaction with a pharmacological product such as a protein, a protein fragment, a polypeptide, or a chimeric molecule including an antibody, a receptor or a binding protein.

**[0064]** The cyclic olefin polymers or the hydrogenation products thereof can be ring-opened homopolymers of cyclic olefin monomers, ring-opened copolymers of cyclic olefin monomers and other monomers, addition homopolymers of cyclic olefin monomers, addition copolymers of cyclic olefin monomers and other monomers, and hydrogenation products of such homopolymers or copolymers. The above cyclic olefin monomers may include monocyclic olefin monomers, and polycyclic olefin monomers including bicyclic and higher cyclic compounds. Examples of the monocyclic olefin monomers suitable for the production of the homopolymers or copolymers of the cyclic olefin monomers are monocyclic olefin monomers such as cyclopentene, cyclopentadiene, cyclohexene, methylcyclohexene and cyclooctene; lower-alkyl derivatives thereof containing, as substituent groups, 1 to 3 lower alkyl groups such as methyl and/or ethyl groups; and acrylate derivatives thereof.

**[0065]** Examples of the polycyclic olefin monomers are dicyclopentadiene, 2,3-dihydrocyclopentadiene, bicyclo[2,2,1]-hepto-2-ene and derivatives thereof, tricyclo[4,3,0,$1^{2,5}$ ]-3-decene and derivatives thereof, tricyclo[4,4,0,$1^{2,5}$]-3-undecene and derivatives thereof, tetracyclo[4,4,0,$1^{2,5}$,$0^{7,10}$]-3-dodecene and derivatives thereof, pentacyclo[6,5,1,$1^{3,6}$,$0^{2,7}$,$0^{9,13}$ 4-pentadecene and derivatives thereof, pentacyclo[7,4,0,$1^{2,5,0}$,$0^{8,13}$,$1^{9,12}$]-3-pentadecene and derivatives thereof, and hexacyclo[6,6,1,$1^{3,6}$,$1^{10,13}$,$0^{2,7}$,$0^{9,14}$]-4-heptadecene and derivatives thereof. Examples of bicyclo[2,2,1]-hepto-2-ene derivatives include 5-methyl-bicyclo[2,2,1]-hepto-2-ene, 5-methoxy-bicyclo[2,2,1]-hepto-2-ene, 5-ethylidene-bicyclo[2,2,1]-hepto-2-ene, 5-phenyl-bicyclo[2,2,1]-hepto-2-ene, and 6-methoxycarbonyl-bicyclo[2,2,1-]-hepto-2-ene. Examples of tricyclo[4,3,0,$1^{2,5}$]-3-decene derivatives include 2-methyl-tricyclo[4,3,0,$1^{2,5}$]-3-decene and 5-methyl-tricyclo[4,3,0,$1^{2,5}$]-3-decene. Examples of tetracyclo[4,4,0,$1^{2,5}$]-3-undecene derivatives include 10-methyl-tetracyclo[4,4,0,$1^{2,5}$]-3-undecene, and examples of tricyclo[4,3,0,$1^{2,5}$]-3-decene derivatives include 5-methyl-tricyclo[4,3,0,$1^{2,5}$]-3-decene.

**[0066]** Examples of tetracyclo[4,4,0,$1^{2,5}$,$0^{7,10}$]-3-dodecene derivatives include 8-ethylidene-tetracyclo-[4,4,0,$1^{2,5}$,$0^{7,10}$]-3-dodecene, 8-methyl-tetracyclo-[4,4,0,$1^{2,5}$,$0^{7,10}$]-3-dodecene, 9-methyl-8-methoxy-carbonyl-tetracyclo[4,4,0,$1^{2,5}$,$0^{7,10}$]-3-dodecene, 5,10-dimethyl-tetracyclo[4,4,0,$1^{2,5}$,$0^{7,10}$]-3-dodecene. Examples of hexacyclo[6,6,1,$1^{3,6}$,$1^{10,13}$,$0^{2,7}$, $0^{9,14}$]-4-heptadecene derivatives include 12-methyl-hexacyclo[6,6,1,$1^{3,6}$,$1^{10,13}$,$0^{2,7}$,$0^{9,14}$]-4-heptadecene and 1,6-dimethyl-hexacyclo[6,6,1,$1^{3,6}$,$1^{10,13}$,$0^{2,7}$, $0^{9,14}$]-4-heptadecene. One example of the cyclic olefin polymer is an addition homopolymer of at least one cyclic olefin monomer or an addition copolymer of at least one cyclic olefin monomer and at least one other olefin monomer (for example, ethylene, propylene, 4-methylpentene-1, cyclopentene, cyclooctene, butadiene, isoprene, styrene, or the like). This homopolymer or copolymer can be obtained by polymerizing the above monomer or monomers, for example, while using as a catalyst a known catalyst which is soluble in a hydrocarbon solvent and is composed of a vanadium compound or the like and an organoaluminum compound or the like (Japanese Patent Application Laid-Open (Kokai) No. HEI 6-157672, Japanese Patent Application Laid-Open (Kokai) No. HEI 5-43663).

**[0067]** Another example of the cyclic olefin polymer is a ring-opened homopolymer of the above monomer or a ring-opened copolymer of the above monomers. It can be obtained by homopolymerizing the above monomer or copolymerizing the above monomers, for example,

while using as a catalyst a known catalyst such as (1) a catalyst composed of a halide or the nitrate of a platinum group metal such as ruthenium, rhodium, palladium, osmium or platinum and a reducing agent or (2) a catalyst composed of a compound of a transition metal such as titanium, molybdenum or tungsten and an organometal compound of a metal in one of Groups I to IV of the periodic table such as an organoaluminum compound or organotin compound (Japanese Patent Application Laid-Open (Kokai) No. HEI 6-157672, Japanese Patent Application Laid-Open (Kokai) No. HEI 5-43663).

**[0068]** The homopolymer or copolymer may contain unsaturated bonds. The homopolymer or copolymer may be hydrogenated using a known hydrogenation catalyst. Examples of the hydrogenation catalyst include (1) Ziegler-type homogeneous catalysts which are each composed of an organic acid salt of titanium, cobalt, nickel or the like and an organometal compound of lithium, aluminum or the like, (2) supported catalysts which are each composed of a carrier such as carbon or alumina and a platinum metal such as palladium or ruthenium supported on the carrier, and (3) catalysts which are each composed of a complex of one of the above-described platinum group metal (Japanese Patent Application Laid-Open (Kokai) No. HEI 6-157672).

**[0069]** In some variations, the device or a portion of the device such as the drug reservoir is made of a material that comprises a rubber. Examples of suitable rubber materials include butyl rubbers such as butyl rubber, chlorinated butyl rubber, brominated butyl rubber, and divinylbenzene-copolymerized butyl rubber; conjugated diene rubbers such as polyisoprene rubber (high to low cis-1,4 bond), polybutadiene rubber (high to low cis-1,4 bond), and styrene-butadiene copolymer rubber; and ethylene-propylene-diene terpolymer rubber (EPDM). Crosslinkable rubber materials may also be used, and may be made by kneading the above-described rubber materials together with additives such as a crosslinking agent, a filler and/or reinforcement, a colorant, or an age resister.

**[0070]** In some variations, the biocompatible material is a biodegradable polymer. Non-limiting examples of suitable biodegradable polymers include cellulose and ester, polyacrylates (L-tyrosine-derived or free acid), poly(β-hydroxyesters), polyamides, poly(amino acid), polyalkanotes, polyalkylene alkylates, polyalkylene oxylates, polyalkylene succinates, polyanhydrides, polyanhydride esters, polyaspartimic acid, polylactic acid, polybutylene digloclate, poly(caprolactone), poly(caprolactone)/poly(ethylene glycol) copolymers, polycarbone, L-tyrosin-derived polycarbonates, polycyanoacrylates,

polydihydropyrans, poly(dioxanone), poly-p-dioxanone, poly(ε-caprolactone-dimethyltrimethylene carbonate), poly(esteramide), polyesters, aliphatic polyesters, poly(etherester), polyethylene glycol/poly(orthoester) copolymers, poly(glutarunic acid), poly(glycolic acid), poly(glycolide), poly(glycolide)/poly(ethylene glycol) copolymers, poly(lactide), poly(lactide-co-caprolactone), poly(DL-lactide-co-glycolide), poly(lactide-co-glycolide)/poly(ethylene glycol) copolymers, poly(lactide)poly(ethylene glycol) copolymers, polyphosphazenes, polyphosphesters, polyphophoester urethanes, poly(propylene fumarate-co-ethylene glycol), poly(trimethylene carbone), polytyrosine carbonate, polyurethane, terpolymer (copolymers of glycolide lactide or dimethyltrimethylene carbonate), and combinations, mixtures or copolymers thereof.

**[0071]** Additives may be added to polymers and polymer blends to adjust their properties as desired. For example, a biocompatible plasticizer may be added to a polymer formulation used in at least a portion of a device to increase its flexibility and/or mechanical strength, or to provide color contrast with respect to the surface of the eye. In other instances, a biocompatible filler such as a particulate filler, fiber and/or mesh may be added to impart mechanical strength and or rigidity to a portion of a device.

**[0072]** The devices described here can be manufactured, at least in part, by injection or compression molding the above-described materials.

**[0073]** In some instances, it may be beneficial to include a removably attached or integrated viewing and/or magnifying element on the device. For example, a magnifying glass and/or illumination source such as a LED light may be removably attached to the device to facilitate the visualization of the tip of the device and the injection site. The improved visualization may help to more precisely and safely position the device at a target location, e.g., about 3.5 mm to 4 mm posterior to the corneo-scleral limbus, so that complications of intraocular injection such as retinal detachment, ciliary body bleeding, or trauma to the intraocular lens can be potentially avoided. The magnifying glass may be made from any suitable material, e.g., it may be made from any suitable non-resorbable (biodegradable) material previously described, but will typically be light-weight so that it does not affect the balance of the injection device. The magnifying glass and/or illumination source, e.g., the LED, may be disposable.

Housing

**[0074]** The housing of the device generally contains the drug reservoir and actuation mechanism. In its first, non-deployed state (pre-deployed state), the conduit may reside within the housing. The housing may be of any suitable shape, so long as it allows grasping and manipulation of the housing with one hand. For example, the housing may be tubular or cylindrical, rectangular, square, circular, or ovoid in shape. In some variations, the housing is tubular or cylindrical, similar to the barrel of a syringe. In this instance, the housing has a length between about 1 cm and about 15 cm, between about 2.5 cm and about 10 cm, or about 4 cm and about 7.5 cm. For example, the housing may have a length of about 1 cm, about 2 cm, about 3 cm, about 4 cm, about 5 cm, about 6 cm, about 7 cm, about 8 cm, about 9 cm, about 10 cm, about 11 cm, about 12 cm, about 13 cm, about 14 cm, or about 15 cm. The surface of the housing may also be texturized, roughened, or otherwise modified in certain areas, e.g., with protrusions, ridges, etc., to aid the grip and or manipulation of the housing by the user.

**[0075]** The housing may be made from any suitable material. For example, and as previously stated, the components of the device may be made from any suitable biocompatible material or combination of biocompatible materials. Materials that may be beneficial in making the housing include, without limitation, a cyclic olefin series resin, a cyclic olefin ethylene copolymer, a polyethylene terephthalate series resin, a polystyrene resin, and a polyethylene terephthalate resin. In one variation, it may be beneficial to use a cyclic olefin series resin and a cyclic olefin ethylene copolymer that have a high transparency, a high heat resistance, and minimal to no chemical interaction with a pharmacological product such as a protein, a protein fragment, a polypeptide, or a chimeric molecule including an antibody, a receptor or a binding protein. Additional materials that may be beneficial in making the housing include, without limitation, fluoropolymers; thermoplastics such as polyetheretherketone, polyethylene, polyethylene terephthalate, polyurethane, nylon, and the like; and silicone. In some variations, the housing may be made from a transparent material to aid confirmation of conduit deployment and/or drug delivery. Materials with suitable transparency are typically polymers such as acrylic copolymers, acrylonitrile butadiene styrene (ABS), polycarbonate, polystyrene, polyvinyl chloride (PVC), polyethylene terephthalate glycol (PETG), and styrene acrylonitrile (SAN). Acrylic copolymers that may be useful include, but are not limited to, polymethyl methacrylate

(PMMA) copolymer and styrene methyl methacrylate (SMMA) copolymer (e.g., Zylar 631® acrylic copolymer).

Ocular Contact Surfaces

**[0076]** The devices described herein generally include an atraumatic ocular contact surface at the distal end of the housing. In some variations, the ocular contact surface is fixedly attached to the housing proximal end. In other variations, the ocular contact surface is removably attached to the housing proximal end. The ocular contact surface will typically be sterile. In some instances, the ocular contact surface is disposable. In use, the ocular contact surface of the device is placed on the surface of the eye.

**[0077]** The ocular contact surface may be of any suitable configuration, e.g., size, shape, geometry, etc., as long as it allows atraumatic placement of the device on the ocular surface. In some variations, the ocular contact surface is ring-shaped (e.g., FIGS. 1A-1B). When the ocular contact surface takes the shape of a ring, it may have a diameter of about 0.3 mm to about 8 mm, about 1 mm to about 6 mm, or about 2 mm to about 4 mm. In other variations, the ocular contact surface is oval or circular in shape.

**[0078]** More specifically, as shown in the front views of FIGS. 1A-1B, the device tip comprises a ring-shaped ocular contact surface where the distance between the inner diameter and outer diameter of the ring forms a rim. In this instance, the ring-shaped ocular contact surface may be configured as having a wider ocular contact surface (10) (rim) and smaller internal opening (12) (FIG. 1A), or narrower ocular contact surface (14) (rim) with larger internal opening (16) (FIG. 1B). The dispensing member (conduit) may be an injection needle that is hidden inside and protected by the device tip. A membrane may also be provided that extends across the internal opening, and which may be flush with the ocular contact surface or recessed within the lumen of the device tip where the injection needle resides.

**[0079]** As shown in FIGS. 39A-39B, the tip of the dispensing member may be recessed relative to end of the device housing tip comprising the ocular contact surface in the resting state, so that when the device tip is placed in contact with any surface such as the skin or the eye wall, the tip of the dispensing member is separated from the surface by a distance marked with arrows in FIG. 39B. This distance may ensure that the dispensing member tip does not come in direct contact with any surface prior to the injection procedure, which prevents

accidental bacterial contamination of the dispensing member from sources such as skin secretions, ocular secretions or tears, and minimizes the risk of introducing intraocular infectious agents during the intraocular injection procedure that may cause endophthalmitis.

**[0080]** In some variations, the tip of the dispensing member is recessed relative to, and is separated from the closest end of the device housing by a distance ranging from about 0.01 mm to about 10 mm, from about 0.1 mm to about 5 mm, or from about 0.5 mm to about 2 mm.

**[0081]** In another variation, the ocular contact surface of the device tip that comes in direct contact with the eye surface is ring-shaped, where there is a clearing between the internal wall of the device housing and the dispensing member of about 360 degrees, which is marked by arrows in FIG. 39C. Here, if the ring-shaped ocular interface surface becomes contaminated with an infectious agent and is placed onto the eye surface, the dispensing member will come in contact and penetrate through the eye surface that is separated from the contaminated device tip by the area of clearing, which prevents accidental bacterial contamination of the dispensing member and minimizes the risk of introducing intraocular infection that may cause endophthalmitis. In contrast, the lack of such clearing around the dispensing member, as shown in FIG. 39D, may allow accidental infectious contamination of the device tip at the site of injection.

**[0082]** In some variations, there is a clearing between the internal wall of the device housing and the dispensing member ranging from about 0.1 mm to about 5 mm, from about 0.3 mm to 3 mm, or from about 0.5 mm to about 2 mm.

**[0083]** In other variations, there is a solid membrane or partition (105) that separates the tip of the dispensing member (107) from the external environment, as shown in FIG. 39E, where the membrane or partition may be water-impermeable and/or be air-impermeable. The membrane or partition may ensure that there is no air movement in or out of the device creating an air seal and maintaining a certain constant air pressure inside the device.

**[0084]** Furthermore, the membrane or partition may ensure that the dispensing member tip does not come in contact with any source of accidental bacterial contamination such as tears and ocular secretions prior to the injection procedure, which prevents accidental bacterial contamination of the dispensing member and minimizes the risk of introducing intraocular infection during the intraocular injection procedure that may cause endophthalmitis.

**[0085]** The membrane or partition that separates the tip of the dispensing member from the end of the device housing may comprise a material selected from the group consisting of biocompatible and non-biodegradable materials including without limitation, methylmethacrylate (MMA), polymethylmethacrylate (PMMA), polyethylmethacrylate (PEM), and other acrylic-based polymers; polyolefins such as polypropylene and polyethylene; vinyl acetates; polyvinylchlorides; polyurethanes; polyvinylpyrollidones; 2-pyrrolidones; polyacrylonitrile butadiene; polycarbonates; polyamides; fluoropolymers such as polytetrafluoroethylene (e.g., TEFLON$^{TM}$ polymer); or fluorinated ethylene propylene (FEP); polystyrenes; styrene acrylonitriles; cellulose acetate; acrylonitrile butadiene styrene; polymethylpentene; polysulfones; polyesters; polyimides; natural rubber; polyisobutylene rubber; polymethylstyrene; silicone; derivatives and copolymers and blends thereof.

**[0086]** In some variations, the membrane or partition (30) may be recessed inside the device tip so that when the device tip is placed in contact with any surface such as the skin or the eye surface, the said membrane or partition is separated from the said surface by a distance marked with arrows, as depicted in FIG. 39E. The distance may ensure that the dispensing member tip (31) does not come in direct contact with any surface prior to the injection procedure, which prevents accidental bacterial contamination of the dispensing member from sources such as skin secretions, ocular secretions or tears, and minimizes the risk of introducing intraocular infection during the intraocular injection procedure that may cause endophthalmitis.

**[0087]** The membrane or partition may be recessed relative to and separated from the end of the device housing at the ocular interface by a distance ranging from about 0.01 mm to about 10 mm, from about 0.1 mm to about 5 mm, or from about 0.5 mm to about 2 mm.

**[0088]** In further variations, a measuring component (32) (further described below) may be recessed relative to the end of the device housing (33) at the ocular contact surface (FIGS. 39F-39H), so that when the device tip (34) comes in contact with the eye surface (35) (FIG. 39I), the measuring component (32) does not come in contact with the eye surface (35). This configuration may minimize the risk of trauma to the delicate tissue covering the eye surface such as the non-keratinizing epithelia of the cornea and conjunctiva. Avoiding direct contact between the measuring member and the ocular surface may be beneficial in minimizing the risk of ocular surface trauma such as corneal or conjunctival abrasion, which prevents further serious complications such as bacterial injection including corneal ulcer. In alternative

variations, the tip of the measuring member (32) may be angled away or towards the eye (FIGS. 39G and 39H, respectively). The measuring component may be recessed relative to the end of the device housing by a distance ranging from about 0.01 mm to about 5 mm, from about 0.1 mm to about 3 mm, or from about 0.5 mm to about 2 mm.

**[0089]** In some variations, as shown in FIGS. 2A-2C, the device tip may also comprise a ring-shaped ocular contact surface and a measuring means that helps to determine the proper location of the injection site at a certain distance relative to and perpendicular to the corneo-scleral limbus. In one variation, the measuring component (20) is located on one side of the device tip (22). In another variation, more than one measuring component is located on more than one side of the device tip. Here the tip of the measuring component is flat (FIG. 2C) and does not substantially protrude above the ocular contact surface. In other variations, the tip of the measuring component is raised (FIGS. 2A-2B) above the ocular contact surface, which enables it to prevent the eyelid from sliding over and on top of the measuring component, thus preventing the eyelid from coming into contact with the sterile ocular contact surface of the device tip or the dispensing member. This in turn may reduce the risk of accidental contamination and intraocular infection during the injection procedure.

**[0090]** In other variations, the ocular contact surface comprises a flange (e.g., FIGS. 3A1-3A3, FIGS. 3B1-3B3, FIG. 4A, and FIGS. 4B1-4B2). The flange may provide an expanded contact surface between the device tip and the eye surface, thus increasing the stability of the device when it is positioned on the ocular surface, and decreasing the pressure force per unit area of the device-ocular interface. Reducing the pressure force per unit area of the device-ocular interface in turn may reduce the potential for conjunctival damage by the device tip when it is pressed against the eye wall. Avoiding such conjunctival damage is desirable because the conjunctiva is covered by delicate non-keratinizing epithelium containing multiple sensory nerve endings and pain receptors.

**[0091]** In some variations, the flange may have thin edges that come in contact with the ocular surface, and which allows the eye lid to travel over and on top of the flange, but prevents the eye lid from coming in contact with the sterile ocular contact surface of the device tip. The ocular contact surface may also be a ring-shaped flange (e.g., FIGS. 4A and 4B1-4B2). Such a ring-shaped flange may also prevent the eye lid from coming in contact with the sterile ocular contact surface of the device tip.

**[0092]** More specifically, as shown in FIG. 3, the flange may have a thin edge (FIG. 3A1), which allows the eye lid to slide over the said flange and come in contact with the shaft of the device tip. In an alternative variation, the said flange may be thick (FIG. 3B1) in order to prevent the eye lid from sliding over it and keeping it from coming in contact with the device shaft, thus preventing inadvertent contamination of the injection site. When the flange at the ocular contact surface of the device tip is thick, its edges, such as those at its ocular surface may be rounded in order to prevent accidental damage to the ocular surface tissues such as the conjunctiva that is covered with delicate non-keratinizing epithelium rich in nerve endings and pain receptors. In alternative variations of the device tip, the ocular contact interface may be flat (FIGS. 3A1 and 3B1), convex (FIGS. 3A2 and 3B2), or concave (FIGS. 3A3 and 3B3) to reduce the chance of accidental damage to ocular surface tissues such as the conjunctiva while providing a means of applying a force onto the eye wall and increasing intraocular pressure in order to facilitate the needle penetration through the eye wall, as well as to partially immobilize the eye during the injection procedure by providing the traction interface of the ocular contact surface. FIGS. 4A and 4B1-4B2 illustrate perspective and front views of a flanged ocular contact surface.

**[0093]** In yet further variations, the ocular contact surface may be configured to be flat, convex, concave, or slanted (e.g., FIGS. 5 and 7). In FIGS. 5A1-5A2, the device tip has a flat ocular contact surface. In an alternative variation, the device tip has a protruding or convex ocular contact surface (FIGS. 5B1-5B2), which may improve contact between the internal opening of the device tip and the ocular surface when the device tip is pressed against the eye wall resulting in eye wall indentation. In yet another variation, the ocular contact surface of the device tip is indented or concave, which reduces the risk of accidental damage to the ocular surface tissue such as the conjunctiva. Such configurations of the ocular contact surface of the device tip may reduce the chance of accidental damage to ocular surface tissues, such as the conjunctiva, while providing a means of applying a pressure force onto the eye wall and increasing the intraocular pressure in order to facilitate the needle penetration through the eye wall, as well as to partially immobilize the eye during the injection procedure by providing the device-ocular surface traction interface.

**[0094]** More specifically, as shown in FIG. 7, the ocular contact surface may be flat and perpendicular to the long axis of the said device (FIGS. 7A1-7A2), or is flat and slanted relative to the long axis of the said device (7B1-7B2) (e.g., oriented at an angle other than 90

degrees, such as from about 45 degrees to about 89 degrees relative to the long axis of the device), or is convex and perpendicular to the long axis of the device (FIG. 7C1), or is convex and slanted relative to the long axis of the device (FIG. 7C2), or is rounded (FIG. 7D), or is oval (FIG. 7E). In one variation, the ocular interface is rounded or oval (e.g., similar to the tip of a Q-tip). The thickness of the ocular contact surface may be from about 0.01 mm to about 10 mm, from about 0.05 mm to about 5 mm, or from about 0.1 mm to about 2 mm.

**[0095]** The ocular contact surface may include one or more features that help to stabilize it on the eye surface. For example, in one variation, the ocular contact surface comprises a plurality of traction elements, e.g., bumps, ridges, etc., that increase surface traction of the ocular contact surface on the eye surface without being abrasive. Such an ocular contact surface may provide a medium- or high-traction interface to stabilize the device on the surface of the eye and prevent it from moving during intraocular drug delivery. In another variation, the ocular contact surface includes an adherent interface such as a suction mechanism. Varying the type of material used to make the ocular contact surface may also help prevent its slippage on the ocular surface.

**[0096]** The materials used to make the ocular contact surface may also help to prevent abrasion, scratching, or irritation of the eye surface. Exemplary non-abrasive materials that may be employed include without limitation, nylon fiber, cotton fiber, hydrogels, spongiform materials, styrofoam materials, other foam-like materials, silicone, plastics, PMMA, polypropylene, polyethylene, fluorinated ethylene propylene (FEP), and polytetrafluoroethylene (PTFE). These materials may be smooth-hard, semi-hard, or soft, and may be beneficial in preventing conjunctival abrasion, subconjunctival hemorrhage during transcleral needle deployment, or other accidental trauma to the ocular surface tissues (FIG. 6). Materials typically used in contact lens manufacturing may also be employed.

**[0097]** In some variations, the edges of the ocular contact surface are also rounded to prevent accidental damage to the ocular surface tissues such as the conjunctiva that is covered with delicate non-keratinizing epithelium rich in nerve endings and pain receptors. In this instance, as shown in FIG. 6, the ocular contact surface may have a circumference corresponding to the circumference of the device tip (FIGS. 6A1-6A2). In other variations, the circumference of the ocular contact surface may protrude beyond the circumference of the shaft of the device tip, thus forming a flange (FIGS. 6B1-6B2). The flange may increase the

ocular contact surface of the device tip while maintaining the slim profile of the shaft of the tip, enabling its easy insertion into the interpalprebral fissure of the eye.

**[0098]** The ocular contact surface may also provide an interface surface that is pliable or deformable, and which conforms to the surface of the eye when placed against the said eye surface during the intraocular drug delivery procedure. The surface of the eye that comes in direct contact with the said interface surface of the disclosed device includes, but is not limited to, the surface of the eye over the pars plana region defined as the circumferential area between about 2 mm and 7 mm posterior to and surrounding the limbus, or the corneo-scleral limbal area between about 2 mm anterior and about 2 mm poster to and circumferential to the limbus. The interface surface that conforms to the curvature of the surface of the eye may enable the formation of an optimal contact interface between the device and the eye, and may ensure sterility of the intraocular drug delivery process and immobilization of the eye, which in turn may enhance the safety of the injection procedure. Examples of ocular interface materials for the device are those that are generally able to conform to the surface of the eye (that is deformable or pliable) particularly to the curvature of the external surface of the eye in the area of pars plana about 2-5 mm posterior to the corneo-scleral limbus for intravitreal drug application, as well as to the area of the corneo-scleral limbus for anterior chamber drug applications. As previously stated, materials that are non-abrasive to the non-keratinizing conjunctival and corneal epithelium of the ocular surface may be used. Specifically, the materials and their configurations (e.g., foam, braid, knit, weave, fiber bundle, etc.), may include those capable of forming medium- or high-traction surfaces (e.g., hydrogels or cotton) that enable immobilization of the eye globe during the injection procedure.

**[0099]** In some variations, the material of the ocular contact surface changes its properties upon contact with fluid, e.g., by reducing its traction coefficient such as in cotton fiber, which may reduce the risk of conjunctival abrasion upon contact of the ocular contact surface with the eye surface. In other variations, the material comprising ocular contact surface does not change its physical and chemical properties when exposed to fluid that covers the surface of the eye such as tears.

**[0100]** The ocular contact surfaces described here may be beneficial in preventing conjunctival and/or episcleral bleeding during intraocular needle injection. For example, a device comprising a ring-shaped ocular interface may be pressed against the eye wall, which

in turn applies pressure to the conjunctival and episcleral vessels, thereby reducing blood flow therethrough. Given the reduced blood flow through these vessels, the risk of subconjunctival bleeding during intraocular injection procedure may be reduced. Following the completion of intraocular drug application, the needle is withdrawn, but the ring-shaped tip may remain pressed against the eye wall, thus applying continuous pressure onto the conjunctival and episcleral vessels and further reducing the risk of bleeding and/or minimizing the extent of bleeding.

**[0101]** In some variations, the device comprises an ocular contact surface that functions as a drug reservoir. Here a drug may be incorporated into, or coated on, the material of the ocular contact surface. The drug may then diffuse, leech, etc., from the ocular contact surface onto the surface of the eye. Exemplary materials for inclusion of drugs are hydrogels and their derivatives.

**[0102]** The ocular contact surface may also cover the dispensing member (conduit) such as an injection needle (e.g., it may be a cap that entirely covers the needle), which may enable the injector to apply pressure onto the eye by pressing the tip (e.g., the distal end of the cap) against the eye wall. This in turn may increase the intraocular pressure before the needle comes in contact with the eye wall and, thus, may facilitate needle penetration because the eye wall is more taut in comparison to an eye wall being penetrated by a needle on a conventional syringe. Needle penetration is typically more difficult with a conventional syringe because the lower intraocular pressure that is generated makes the eye wall more deformable and mobile. In addition, the device tip that covers the dispensing member (conduit), such as an injection needle, may also protect the said dispensing member from being contaminated by its accidental contact with eye lids.

Intraocular Pressure Control Mechanisms (Ocular Wall Tension Control Mechanisms)

**[0103]** The control of intraocular pressure (IOP) during the drug delivery procedure, e.g., intraocular injection or intravitreal injection, may be beneficial. The application of limited intraocular pressure before deployment of the dispensing member (conduit) may reduce scleral pliability, which in turn may decrease any unpleasant sensation on the eye surface during an injection procedure and/or prevent backlash of the device. The term "backlash" typically refers to the inability of the conduit to smoothly penetrate the eye wall due to scleral

pliability and elasticity, which makes the sclera indent to a certain point and push the conduit and device backwards before the conduit penetrates into and through the sclera. Accordingly, the devices described here may include one or more IOP control mechanisms, also referred to herein as ocular wall tension control mechanisms. This is because ocular wall tension is proportionally related to, and determined in part, by intraocular pressure. Other factors that may effect wall tension are scleral thickness and rigidity, which can be variable due to patient age, gender, and individual variations.

**[0104]** The IOP mechanisms may control IOP during the placement and positioning of the device tip at the target location on the ocular surface, and/or intraocular or intravitreal positioning of the dispensing member (conduit) during intraocular or intravitreal injection of a drug. For example, the IOP mechanisms may control IOP prior to and during the intraocular or intravitreal positioning of a dispensing member being used for trans-scleral or trans-corneal penetration. Once penetration of the ocular surface by the dispensing member occurs, IOP will typically decrease. This decrease in IOP may occur immediately after penetration of the ocular surface by the dispensing member.

**[0105]** In some variations, the IOP control mechanisms allow (enable) the devices to generate an IOP between 15 and 120 mm Hg during the placement and positioning of the device tip at a target location on the ocular surface, and/or intraocular positioning of the dispensing member. In other variations, the IOP control mechanisms allow (enable) the devices to generate an IOP between 20 and 90 mm Hg during the placement and positioning of the device tip at a target location on the ocular surface, and/or intraocular positioning of the dispensing member. In yet further variations, the IOP control mechanisms allow (enable) the devices to generate an IOP between 25 and 60 mm Hg during the placement and positioning of the device tip at a target location on the ocular surface, and/or intraocular positioning of the dispensing member.

**[0106]** The IOP control mechanisms may also allow (enable) the devices to maintain the IOP between 10 and 120 mm Hg, or between 15 and 90 mm Hg, or between 20 and 60 mmHg during any duration of time of the intraocular injection procedure. In some variations, the drug injection rate is slowed or completely aborted by the device if the intraocular pressure exceeds a certain predetermined value, for example 120 mm Hg, or 60 mm Hg, or 40 mm Hg. Here the IOP control mechanism may be configured to detect a IOP level during the intraocular drug injection of, e.g., 90 mmHg, or 60 mm Hg, or 40 mm Hg.

**[0107]** The IOP control mechanism may include a spring, or it may comprise a mechanical or an electrical control mechanism. In general, the IOP control mechanism will be configured to balance the frictional forces of the injection plunger and fluid injection resistance pressure (force required to push fluid through the needle into the pressurized eye fluids). The IOP control mechanisms may be coupled to the device housing and actuation mechanism in a manner that allows automatic adjustment of the force of dispensing member deployment and plunger advancement. That is, the IOP control mechanism may be configured to effect a predetermined level of force of the dispensing member and a predetermined intraocular pressure level. Again, use of the IOP control mechanisms may generate higher than the resting IOP prior to dispensing member deployment so that scleral elasticity and the potential for device backlash is decreased, and to facilitate scleral penetration by the dispensing member.

**[0108]** In one variation, the IOP control mechanism is a pressure relief valve that bypasses the injection stream once a maximum pressure is reached. In another variation, the IOP mechanism is a pressure accumulator that dampens the IOP within a specified range. Some variations of the IOP control mechanism may include a pressure sensor. In yet another variation, the IOP control mechanism includes a slidable cap that covers the dispensing member prior to its deployment, but which may slide or retract along the surface of the device housing to expose, deploy, or advance the dispensing member e.g., upon attainment of a predetermined IOP level. Sliding of the cap may be manually adjustable, e.g., using a dial, or automatically adjustable, step-wise, or incremental in nature. For example, as shown in FIG. 40, integrated injection device (500) includes, among other elements, a cap (502), a stop (504), a trigger (506), a spring (508), a plunger (510), a seal (512), a drug reservoir (514), a needle (516), and a syringe (518). In use, when cap (502) is placed against the ocular surface and pressure applied against the ocular surface, cap (502) slidably retracts proximally (in the direction of the arrow) to stop (504) as the syringe (518) and needle (516) are advanced. The trigger (506), e.g., a lever, may then be depressed to release spring (508), which advances plunger (510) and seal (512) to inject drug from the drug reservoir (514) through needle (516). Once the drug is injected, cap (502) slides back over the needle (516).

**[0109]** A locking mechanism may also be used to prevent sliding of the cap, cover or ocular contact surface, or prevent deployment of the dispensing member until a predetermined IOP is reached. The locking mechanism may also be used to prevent sliding

of the cap, cover, or ocular contact surface if a predetermined IOP is not reached. For instance, the locking mechanisms included on the devices described here that include a slidable cover, cap, etc., may be released manually or automatically when the IOP reaches a predetermined level, such as between 20 mm Hg and 80 mm Hg. Such locking mechanisms may include without limitation, high traction surfaces, locking pins, interlocking raised ridges, or any other type of locking mechanism that prevents the tip of the device, e.g., the cap or cover of the device, from sliding and thus exposing the needle.

**[0110]** In yet further variations, the IOP control mechanism includes a high-traction surface or raised ridges on the cap, cover, or ocular contact surface situated over the dispensing member. Such features may be disposed on the inner surface of the cap, cover, or ocular contact surface and configured so that upon sliding in the proximal direction, the high-traction surface or raised ridges mate with corresponding structures (e.g., crimps, dimples, protrusions, other raised ridges) on the surface of the device housing or other appropriate device component to provide resistance of the cap, cover, or ocular contact surface against the eye wall (thus increasing ocular wall tension and IOP). In this instance, the IOP control mechanism comprises a dynamic resistance component, as further described below. As stated above, the cap, cover, or ocular contact surface may be configured so that sliding is manually or automatically adjustable, step-wise, or incremental in nature. When raised ridges are employed, any suitable number may be used, and they may be of any suitable size, shape, and geometry. For example, the raised ridges may be circumferentially disposed within the cap, cover, or ocular contact surface. In some instances, the raised ridges are configured with surfaces of differing slope. For example, the distal surface may be configured to be steeper than the proximal surface. With this design, incremental sliding and incremental increases in IOP may be generated when the cap, cover, or ocular contact surface is slid proximally, but sliding of the cap, cover, or ocular contact surface back over the dispensing member may also be accomplished due to the decreased slope of the proximal ridge surface.

Dynamic Resistance Component

**[0111]** The application of pressure to the surface of the eye may be accomplished and further refined by including a dynamic resistance component to the injection device. The dynamic resistance component may include a slidable element coupled to the housing. In some variations, the slidable element comprises a dynamic sleeve configured to adjust the

amount of pressure applied to the eye surface, as further described below. As previously stated, certain variations of the ocular wall tension control mechanism function as dynamic resistance components.

**[0112]** The dynamic resistance component may also be configured as a dynamic sleeve. Similar to the slidable cap previously described, the dynamic sleeve may be configured to increase intraocular pressure and tension of the eye wall prior to needle injection. However, the dynamic sleeve is capable of being manually manipulated to thereby adjust the amount of pressure applied on surface of the eye (and thus, the amount of eye wall tension). Having the ability to manually adjust the applied pressure may allow the injector (user) to have improved control of the injection site placement and the injection angle, and also enhances the user's ability to stably position the device on the ocular surface prior to needle deployment. In general, the dynamic sleeve is designed to enable the user to precisely position the device tip at the targeted site on the eye surface and to firmly press the device tip against the eye wall to increase wall tension and intraocular pressure. The dynamic sleeve may be used to raise intraocular pressure to a predetermined level, as described above, prior to the initiation of sleeve movement and needle deployment. It should be understood that the terms "dynamic sleeve," "sleeve," "dynamic sleeve resistance control mechanism," and "sleeve resistance mechanism" are used interchangeably throughout. The dynamic sleeve will generally be configured such that when the user exerts a pulling force (e.g., retraction) on the sleeve, this movement may facilitate needle exposure and reduce the amount of pressure force (down to 0 Newton) ("N" refers to the unit of force "Newton") needed to be applied to the eye wall in order to slide the sleeve back and expose the needle. The dynamic sleeve may also be configured such that when the user exerts a pushing force (e.g., advancement) on the sleeve, this movement may counteract and impede needle exposure, which may allow the device tip to apply increased pressure to the eye wall prior to the initiation of sleeve movement and needle exposure.

**[0113]** Some variations of the dynamic sleeve provide a variable force that follows a U-shaped curve, as described further in Example 1 and FIG. 46. Here the highest resistance is encountered at the beginning and the end of dynamic sleeve movement along the housing with decreased resistance between the start and end points of dynamic sleeve travel. In use, this translates to having an initial high-resistance phase (upon initial placement on the eye wall) followed by a decrease in resistance to sleeve movement during needle advancement

into the eye cavity. When the needle is fully deployed, the dynamic sleeve will typically be at the end of its travel path, and increased resistance would again be encountered. This increase in resistive force allows the sleeve to come to a smooth, gradual stop (instead of an abrupt hard stop at the end point) to minimize the risk of transmitting damaging amounts of force to the inert eye wall (which in turn minimizes the risk of causing discomfort or injury to the eye). Here an exemplary dynamic sleeve may be configured to be tapered at the proximal end and distal end. Referring to the sectional view in FIG. 42, integrated injection device (42) includes a housing (44), a resistance band (46) wholly or partially surrounding the housing, and a dynamic sleeve (48) that can be slidably advanced and retracted upon the housing (44). The dynamic sleeve (48) has a proximal end (50) and a distal end (not shown) that are tapered. The tapered ends may provide higher traction at the beginning and the end of the dynamic sleeve travel path along the device housing (44) (that is at the beginning and end of needle deployment). The taper at the proximal end (50) provides higher traction and resistance at the beginning of dynamic sleeve movement when it contacts resistance band (46). The thickness of the resistance band (46) may be varied to adjust the amount of resistance desired. Upon reaching the wider middle segment (52), lower-traction and lower resistance movement is encountered, followed by higher traction and higher resistance at the end of needle deployment as the taper at the distal end of the dynamic sleeve is reached. As the dynamic sleeve becomes progressively more tapered at the distal end, more traction is produced against the device housing until it gradually comes to a complete stop. Instead of both ends being tapered, in some variations one of the proximal end and distal end of the dynamic sleeve may be tapered.

**[0114]** Variable traction force may also be provided by components such as circular raised bands or ridges on the outside surface of the device tip. These components may provide counter-traction when approximated against another circular raised band or ridge on the inside surface of the movable dynamic sleeve (inner bands or ridges). When the outer and inner bands or ridges are in contact with each other before the dynamic sleeve begins to move, they generate high traction and high resistance to dynamic sleeve movement. Once the dynamic sleeve starts to move, the raised band on the outside of the device housing moves past the raised band on the inside of the dynamic sleeve, which may result in a rapid decrease in resistance to dynamic sleeve movement and, therefore, decreased pressure on the eye wall by the device tip. The shape of the raised interlocking bands or ridges will generally

determine the shape of resistance decrease. For example, the resistance decrease may follow a sine-shaped profile.

**[0115]** In another variation, the dynamic sleeve may generate a force that continuously decreases from its highest point before needle deployment (when the dynamic sleeve completely covers the needle), to its lowest point when the dynamic sleeve begins to move to expose the needle tip. Here the force remains low until the end of dynamic sleeve travel and complete needle deployment. This pattern of resistance decrease may follow a sine-shaped curve.

**[0116]** Slidable advancement of the dynamic sleeve may generate a force between itself and the housing ranging from 0 N to about 2 N. In some instances, slidable advancement of the dynamic sleeve generates a force between itself and the housing ranging from about 0.1 N to about 1 N.

Measuring Components

**[0117]** The devices described here may include a measuring component that may be useful in determining the location of the intraocular injection site on the eye surface. Integrated devices will generally include a measuring component. The measuring component may be fixedly attached or removably attached to the ocular contact surface. As previously stated, the measuring component may be raised above the ocular surface so that it prevents the eye lid from coming in contact with the sterile ocular contact surface of the device tip (e.g., FIGS. 2A-2B and 8). The specific configuration of the measuring component may also help to minimize the risk of inadvertent contamination of the sterile drug dispensing member (conduit) such as an injection needle. Such contamination may result from various causes such as the sterile needle coming in inadvertent contact with an eyelid or other non-sterile surface. The measuring components may also be colored in a manner to provide color contrast against the surface of the eye including the conjunctiva, the sclera, and the iris.

**[0118]** In general, the measuring component will enable the intraocular injection site to be more precisely placed at a specific distance from, and posterior or anterior to, the corneal-scleral junction termed "the limbus." In some variations, the measuring component may provide for placement of the intraocular injection site from about 1 mm to about 5 mm, from about 2 mm to about 4.5 mm, or from about 3 mm to about 4 mm, from and posterior to the limbus. In another variation, the measuring component may provide for placement of the

intraocular injection site from about 2 mm to about 5 mm posterior to the limbus, or about 3.5 mm posterior to the limbus. In other variations, the measuring component may provide for placement of the intraocular injection site from within about 3 mm or about 2 mm, from and anterior to, the limbus, or between about 0.1 mm and about 2 mm from and anterior to the limbus. In one variation, the measuring component provides for placement of the intraocular injection site between about 1 mm anterior to the limbus and about 6 mm posterior to the limbus. In another variation, the measuring component provides for placement of the intraocular injection site between about 3 mm to about 4 mm posterior to the limbus.

**[0119]** The measuring components may have any suitable configuration. For example, the measuring components may be located on one side of the ocular contact surface or on more than one side of the ocular contact surface (e.g., FIGS. 9, 10, and 11). Here, when the tip of the measuring component is placed right next to the corneo-scleral limbus, the site of the intraocular needle injection is placed at a particular distance from the limbus, e.g., between about 3 mm and about 4 mm posterior to the limbus.

**[0120]** In alternative variations, the measuring component comprises one or more members (e.g., FIGS. 9, 10, and 11). These members may radially extend from the ocular contact surface. Having more than one member comprise the measuring component may be beneficial in ensuring that the distance between the limbus and injection site is measured perpendicular to the limbus and not tangentially as it may be the case when the measuring means comprise a single member. When the tips of all members comprising the measuring component are aligned along the corneo-scleral limbus, the site of the intraocular needle injection is placed at a particular distance from the limbus, such as between about 3 mm and about 4 mm posterior to the limbus.

**[0121]** More specifically, as shown in FIG. 8, the device tip having an ocular contact surface comprises a measuring component (80) that enables the determination of the injection site at a certain distance relative to the corneo-scleral limbus. As previously stated, in one variation the measuring component is located on one side of the device tip. In another variation, more than one measuring component is located on more than one side of the device tip. In yet further variations, the tip of the measuring component may be raised, bent, etc., which prevents the eye lid from sliding over the measuring component and coming in accidental contact with the dispensing member (conduit) of device. Also in FIG. 8, the dispensing member (conduit) is shown as being completely shielded inside the device tip.

**[0122]** FIG. 9 provides further detail about another variation of the measuring component. Here the device tip comprises a ring-shaped ocular contact surface (90) and a measuring component (91) that enables the determination of the injection site at a certain distance relative to the corneo-scleral limbus. The outer circumference of the device tip that comes into contact with the surface of the eye has, e.g., a ring shaped ocular interface, and the dispensing member such as an injection needle may be hidden inside and protected by the device tip. In FIG. 9, the measuring components (91) are located on one side of the device tip (FIGS. 9A-9B) or on more than one side of the device tip (FIG. 9C). Thus, when the tip of the measuring component is placed next to the corneo-scleral limbus, the site of intraocular needle injection is placed at a specific distance from the limbus, such as between about 3 mm and about 4 mm posterior to the limbus. Any suitable number of measuring components may be provided on the device tip, e.g., attached to the ocular contact surface. When a plurality of measuring components are used, they may be arranged around the ocular contact surface in any suitable fashion. For example, they may be circumferentially disposed around the ocular contact surface or on one side of the ocular contact surface. They may be equally or unequally spaced around the circumference of the ocular surface. In other variations, the measuring components may be symmetrically spaced or asymmetrically spaced around the circumference of the ocular contact surface. These configurations may be beneficial in allowing the injector to rotate the device along its long axis.

**[0123]** FIGS. 10A-10C provide additional views of measuring components that are similar to those shown in FIGS. 9A-9C. In FIG. 10, a ring-shaped ocular contact surface (93) is shown having a measuring component (93) that enables the determination of the injection site at a certain distance relative to and perpendicular to the corneo-scleral limbus (94). The measuring components are depicted on one side of the device tip, or in another variation, on more than one side of the device tip. Again, the measuring components may comprise one or more members. Having more than one member comprise the measuring component may be beneficial in ensuring that the distance between the limbus and injection site is measured perpendicular to the limbus and not tangentially as it may be the case when the measuring component comprise a single member. When the tips of all members comprising the measuring component are aligned along the corneo-scleral limbus, the site of the intraocular needle injection is placed at a particular distance from the limbus, such as between about 3 mm and about 4 mm posterior to the limbus.

**[0124]** More than one measuring component is also shown in FIGS. 11A-11D. Here the measuring components (95) are depicted as extending from a common attachment point (96) on the ocular contact surface. When the tips of all members comprising the said measuring component are aligned along the corneo-scleral limbus, the site of the intraocular needle injection is placed at a particular distance from the limbus, such as between about 3 mm and about 4 mm posterior to the limbus.

**[0125]** Alternatively, the measuring components may be configured as one or more flexible measuring strips. Flexible materials that may be used to make the measuring strips include flexible polymers such as silicones. As shown in FIG. 44A, the measuring strip (800) may extend from the device tip (802), usually from the side of the ocular contact surface (804), so that the distance between the limbus and injection site can be measured perpendicular to the limbus. A positional indicator component (806) may be employed to ensure that the measuring strip (800) is properly used. For example, as shown in FIG. 44B, correct positioning of the measuring strip (800) (so that a 90 degree angle is formed between the measuring strip and device housing (808)) may be determined when the positional indicator component is substantially taut. In contrast, a slack positional indicator component (as shown in FIG. 44C) would indicate incorrect positioning. The positional indicator component may be a cord. In one variation, the integrated device comprises at least three measuring strips. In another variation, the integrated device includes at least four measuring strips. When a plurality of measuring strips are used, they may be configured in any suitable manner around the tip of the integrated device (equally spaced around the circumference of the ocular contact surface, symmetric or asymmetrically placed around the circumference of the ocular contact surface, etc.). For example, as shown in FIG. 44D, the measuring strips may be configured to span the desired 90 degree angle (45 degrees plus 45 degrees between the farthest strips) to allow for a 90 degree rotation of a control lever without having to reposition the hand of the user.

**[0126]** In some variations, the measuring component may be configured as a marking tip member (97). As shown in FIG. 12, the marking tip member (97) at its distal end (closer to the eye) that interfaces with the ocular surface and leaves a visible mark (98) on the conjunctival surface when pressed against it (e.g., FIG. 13). The marker-tip enables intraocular injections to be carried out through a safe area of the eye relative to the corneo-scleral limbus (99), such as between about 3 mm and about 4 mm posterior to the limbus,

over the pars plana region of the ciliary body of the eye. The diameter of the marking tip may range from about 1 mm to about 8 mm, or from about 2 mm to about 5 mm, or from about 2.3 mm to about 2.4 mm (e.g., FIG. 12).

Conduits

**[0127]** The intraocular drug delivery devices described here may include any suitable conduit (or dispensing member) for accessing the intraocular space and delivering active agents therein. The conduits may have any suitable configuration, but will generally have a proximal end, a distal end, and a lumen extending therethrough. In their first, non-deployed (pre-deployed) state, the conduits will generally reside within the housing. In their second, deployed state, i.e., after activation of the actuation mechanism, the conduit, or a portion thereof, will typically extend from the housing. By "proximal end" it is meant the end closest to the user's hand, and opposite the end near the eye, when the devices are positioned against the eye surface.

**[0128]** The distal end of the conduit will generally be configured to be sharp, beveled, or otherwise capable of penetrating the eye surface, e.g., the sclera. The conduit employed may be of any suitable gauge, for example, about 25 gauge, about 26 gauge, about 27 gauge, about 28 gauge, about 29 gauge, about 30 gauge, about 31 gauge, about 32 gauge, about 33 gauge, about 34 gauge, about 35 gauge, about 36 gauge, about 37 gauge, about 38 gauge, or about 39 gauge. The wall of the conduit may also have any suitable wall thickness. For example, in addition to regular wall (RW) thickness, the wall thickness of the conduit may be designated as thin wall (TW), extra/ultra thin wall (XTW/UTW), or extra-extra thin wall (XXTW). These designations are well known to those of skill in the relevant art. For example, the conduit may be a fine gauge cannula or needle. In some variations, the conduits may have a gauge between about 25 to about 39. In other variations, the conduits may have a gauge between about 27 to about 35. In yet further variations, the conduits may have a gauge between about 30 to about 33.

**[0129]** The conduits may have a sharp, pointed tip (FIGS. 14B-14C and FIGS. 15A1-15A2), rather than a rounded one (FIG. 14A) as in conventional needles. The pointed needle tip is formed by the lateral side surfaces that are straight at the point of their convergence into the tip, and at the point of their convergence forming a bevel angle (the angle formed by the bevel and the shaft of the needle), which may range from between about 5 degrees and about

45 degrees (FIG. 14B), between about 5 degrees and about 30 degrees, between about 13 degrees to about 20 degrees, or between about 10 degrees and about 23 degrees (FIG. 14C).

**[0130]** The sharp, pointed needle tip may provide improved penetration of the needle through the fibrillar, fibrous scleral tissue, which is the major structural cover of the eye and consists of a network of strong collagen fibers. Thus, such a needle tip during its penetration through the eye wall may create less resistance and, thus, decrease the impact force that is transmitted to the intraocular structures, such as the retina and the crystalline lens, in turn causing less damage to intraocular structures during the intraocular injection process (compared to conventional needles).

**[0131]** In addition, such a narrow bevel angle may enable the needle to cause less sensation when it penetrates through the eye wall (the outer cover of the said eye wall being richly innervated with sensory nerve fibers endings particularly densely located in the conjunctiva and cornea), which may be an issue when intraocular injections are involved compared to other less sensitive sites.

**[0132]** The narrow bevel angle may also allow for a longer bevel length and larger bevel opening and, thus, a larger opening at the distal end of the injection needle. With such a configuration, the force of drug injection into an eye cavity may be reduced, thus reducing the chances of intraocular tissue damage by a forceful stream of injected substance, which may occur with conventional short-beveled needles.

**[0133]** In some variations, the conduits are injection needles having one or more flat surface planes, as well as one or more side-cutting surfaces, as illustrated in FIGS. 16 and 17. Examples include a needle shaft comprising multiple surface planes separated by sharp ridges (FIGS. 16A-16C), as well as a needle tip comprising sharp side-cutting surfaces located on either side of the beveled surface of the needle about 90 degrees from the beveled surface (FIG. 17). The conduit may also be bi-beveled, i.e., have two bevels facing about 180 degrees from each other that is located on the opposite sides of the conduit. The conduit may also be coated (e.g., with silicone, PTFE, etc.) to facilitate its penetration through the eye wall.

**[0134]** In other variations, the conduit may be configured to be wholly or partially flattened in at least one dimension, as shown in the cross-sectional view of FIG. 18C taken along the line A—A of FIG. 18A. For example, the conduit may be flattened in the anterior-posterior

dimension (that is from the beveled side of the needle towards its opposite side. In one variation, both the external and internal surfaces of the needle are flattened and represent ovals on cross-section. In another variation, the internal surface of the needle is round and represents a circle on cross-section, while the external surface of the needle is flattened to enable its easier penetration through the fibrous scleral or corneal tissue of the eye wall. In another variation, more than one external surface plane of the needle is flattened to enable its easier penetration through the fibrous eye wall, while the internal opening of the said needle may be of any shape including round or oval.

**[0135]** As previously stated, in its second, deployed state, the conduit or needle extends from the housing. The portion of the needle that extends from the housing can be referred to as the exposed needle length. Upon activation of the actuation mechanism, the needle goes from its first, non-deployed state (pre-deployed state) (where it is entirely within the housing of the device), to its second, deployed configuration outside the housing, where a certain length of it is exposed. This exposed length may range from about 1 mm to about 25 mm, from about 2 mm to about 15 mm, or from about 3.5 mm to about 10 mm. These exposed needle lengths may enable complete intraocular penetration through the sclera, choroid and ciliary body into the vitreous cavity, while minimizing the risk of intraocular damage. In some variations, the exposed needle length ranges from about 1 mm to about 5 mm, or from about 1 mm to about 4 mm, or from about 1 mm to about 3 mm. Here the exposed needle lengths may enable complete intraocular penetration through the cornea into the anterior chamber, while minimizing the risk of intraocular damage.

**[0136]** In some variations, the devices may include an exposure control mechanism (9) for the dispensing member (11) (conduit) (FIGS. 19 and 20). The exposure control mechanism (9) generally enables one to set the maximal length of the dispensing member exposure during dispensing member deployment. In one variation, the exposure control mechanism works by providing a back-stop for the needle-protective member (13). In another variation, the exposure control mechanism (9) may be a rotating ring member with a dialable gauge. Needle exposure could be adjusted by the millimeter or a fraction of the millimeter, e.g., 1 mm, 1.5 mm, 2 mm, 2.5 mm, 3 mm, etc. Here the device may be equipped with a retraction mechanism that controls needle retraction into a needle-protective member. Such a needle-retraction mechanism may be spring-actuated (FIG. 20).

**[0137]** The devices may also include a removable distal (towards the eye) member that covers and protects the conduit (e.g., the front cover (15) in Figure 21). In one variation, the devices may also include a removable proximal (away the eye) member that covers and protects the proximal part of the device, e.g., comprising a loading dock mechanism (17) (e.g., the back cover (19) in Figure 21).

Reservoirs

**[0138]** The reservoir is generally contained within the housing and may be configured in any suitable manner, so long as it is capable of delivering an active agent to the intraocular space using the actuation mechanisms described herein. The reservoir may hold any suitable drug or formulation, or combination of drugs or formulations to the intraocular space, e.g., the intravitreal space. It should be understood that the terms "drug" and "agent" are used interchangeably herein throughout. In one variation, the drug reservoir is silicone oil-free (lacks silicone oil or one of its derivatives) and is not internally covered or lubricated with silicone oil, its derivative or a modification thereof, which ensures that silicone oil does not get inside the eye causing floaters or intraocular pressure elevation. In another variation, the drug reservoir is free of any lubricant or sealant and is not internally covered or lubricated with any lubricating or sealing substance, which ensures that the said lubricating or sealing substance does not get inside the eye causing floaters or intraocular pressure elevation.

**[0139]** In some variation, the reservoir is made of a material that contains a cyclic olefin series resin, a cyclic olefin ethylene copolymer including commercially available products such as Zeonex® cyclo olefin polymer (ZEON Corporation, Tokyo, Japan) or Crystal Zenith® olefinic polymer (Daikyo Seiko, Ltd., Tokyo, Japan) and APEL™ cyclo olefin copolymer (COC) (Mitsui Chemicals, Inc., Tokyo, Japan), a cyclic olefin ethylene copolymer, a polyethylene terephthalate series resin, a polystyrene resin, a polybutylene terephthalate resin, and combinations thereof. In one variation, it may be beneficial to use a cyclic olefin series resin and a cyclic olefin ethylene copolymer that have a high transparency, a high heat resistance, and minimal to no chemical interaction with a pharmacological product such as a protein, a protein fragment, a polypeptide, or a chimeric molecule including an antibody, a receptor or a binding protein.

**[0140]** Exemplary agents may be selected from classes such as anti-inflammatories (e.g., steroidal and non-steroidal), anti-infectives (e.g., antibiotics, antifungals, antiparasitics,

antivirals, and antiseptics), cholinergic antagonists and agonists, adrenergic antagonists and agonists, anti-glaucoma agents, neuroprotection agents, agents for cataract prevention or treatment, anti-oxidants, antihistamines, anti-platelet agents, anticoagulants, antithrombics, anti-scarring agents, anti-proliferatives, anti-tumor agents, complement inhibitors (e.g., anti-C5 agents, including anti-C5a and anti-C5b agents), vitamins (e.g., vitamin B and derivatives thereof, vitamin A, depaxapenthenol, and retinoic acid), growth factors, agents to inhibit growth factors, gene therapy vectors, chemotherapy agents, protein kinase inhibitors, tyrosine kinase inhibitors, PEGF (pigment epithelial growth factor), small interfering RNAs, their analogs, derivatives, conjugates, and modifications thereof, and combinations thereof.

**[0141]** Non-limiting, specific examples of drugs that may be used alone or as part of a combination drug therapy include Lucentis™ (ranibizumab), Avastin™ (bevacizumab), Macugen™ (pegaptanib), steroids, e.g., dexamethasone, dexamethasone sodium phosphate, triamcinolone, triamcinolone acetonide, and fluocinolone, taxol-like drugs, integrin or anti-integrin agents, vascular endothelial growth factor (VEGF) trap (aflibercept), anecortave acetate (Retaane), and limus family compounds. Non-limiting examples of members of the limus family of compounds include sirolimus (rapamycin) and its water soluble analog SDZ-RAD, tacrolimus, everolimus, pimecrolimus, and zotarolimus, as well as analogs, derivatives, conjugates, salts, and modifications thereof, and combinations thereof.

**[0142]** Topical anesthetic agents may also be included in the reservoirs. For example, lidocaine, proparacaine, prilocaine, tetracaine, betacaine, benzocaine, ELA-Max®, EMLA® (eutectic mixture of local anesthetics), and combinations thereof may be used.

**[0143]** The reservoirs and devices described here may be suitable for intraocular administration of a very small volume of a solution, suspension, gel or semi-solid substance. For example, a volume between about 1 μl and about 200 μl, or between about 10 μl and about 150 μl, or between about 20 μl and about 100 μl may be delivered. To that end, the device will generally have a very small "dead space," which enables intraocular administration of very small volumes.

**[0144]** The device reservoirs may be pre-loaded during the manufacturing process or loaded manually before the intraocular injection, as further described below.

Drug Loaders

**[0145]** When a drug or formulation is to be loaded into the reservoir of the device prior to intraocular injection, a loading member may be employed. The loading member may be removably attached to the distal end of the housing. For example, the loading member may function as a loading dock that quantitatively controls the volume of a liquid, semi-liquid, gelatinous, or suspension drug that is to be loaded into the device. For example, the loading member may comprise a dial mechanism (21) that allows the operator to preset a particular volume of a drug to be loaded into the device (FIGS. 21 and 22). The loading may occur with a precision raging from about 0.01 µl and about 100 µl, or from about 0.1 µl and 10 µl. Such a loading member may allow for loading the device reservoir with a liquid, semi-liquid, gelatinous or suspended drug in a particular volume equal or less than that of the drug storage container, which allows for airless loading of the drug into the device. This may be beneficial because air injected into the eye will result in the sensation of seeing "floaters" by the patient, which may be uncomfortable and distracting to the patient particularly during driving or other similar activities.

**[0146]** As shown in FIG. 22, the drug loading mechanism (23) includes a wide base member (25) for upright loading of the reservoir (27) through its proximal (further from the eye) end (29). Also shown are exemplary front (31) and back (33) covers, as well as a dialable control mechanism (21) for setting the loading and/or injection volume(s). In other variations, the devices comprise a loading mechanism such as a loading dock (35A), wherein the dock (35A) interfaces with a drug storage container (FIGS. 25A-25B) such as a vial known to those skilled in the art and penetrates through the vial stopper to gain access to the drug contained inside the vial so that the drug could be loaded into the device reservoir. In FIGS. 25A-25B, the dock mechanism is located in the dependant position so that the drug vial (37) is positioned directly above the dock so that the drug moves from the vial downward in the direction of gravity.

**[0147]** In one variation, the dock mechanism comprises a needle or a sharp cannula that has openings or fenestrations (39) at its base. The said openings or fenestrations are positioned immediately adjacent to the internal aspect of the vial stopper when the loading dock penetrates into the drug vial while in the desired loading position, which in turn enables airless drug loading into the device as well as complete drug removal from the storage container. Airless drug loading may be beneficial because it may prevent the patient from

seeing small intraocular air bubbles or "floaters." Complete drug removal is also beneficial given that small drug volumes and expensive medications are typically used.

**[0148]** In other variations, for example, when the devices have a flat side surface (FIGS. 24A-24D) or a flat front or back surface (FIG. 22), the loading mechanism includes a loading dock located 180 degrees from the flat surface. This results in a loading dock pointing straight upwards, which enables its penetration into a drug container in the dependent position, which in turn enables airless drug delivery into the device, as well as complete drug removal from the storage container and its loading into the said device without drug retention and loss in the storage container.

**[0149]** In further variations, as shown in FIGS. 33A-33B, an access port (144) may be provided at the distal end of the needle assembly (125) that allows drug from a storage container (146) to be loaded into the reservoir (122). Access port (144) may be placed at any suitable location on the needle assembly (125) or housing (102). For example, if desired, the access port may be placed in the front wall of the housing or even the ocular contact surface (not shown) so that drug loading occurs from the front of the device. Access port (144) may be made from a material, e.g., silicone, that allows sealable penetration by a sharp conduit. One or multiple membranes (148) may also be provided, e.g., in the ocular contact surface (108) to seal the internal compartment of the housing against air leak and/or external bacterial contamination. One or multiple small apertures (150) may also be included in the wall of the housing (102) to help control air outflow from the housing (102). The number and diameter of the apertures (150) may be varied to control the rate of (needle assembly and) needle deployment.

**[0150]** In some variations, e.g., when a pneumatic actuation mechanism is used, drug loading may be controlled by a drug-loading piston. For example, as shown in FIG. 38, the device (400) may include a drug-loading piston (402) having a proximal end (404) and a distal end (406). The distal end (406) is adapted to include a threaded portion (408). Thus, during loading of a drug from container (410) through adaptor (412) and access port (414), the drug-loading piston (402) can be rotated and withdrawn to create negative pressure within the reservoir (416). This negative pressure in turn draws the drug through the needle (418) and into the reservoir (416). A receptacle (420) may also be provided at the distal end of the device for holding initially loaded drug prior to transfer into the reservoir (416).

Actuation Mechanisms

**[0151]** The devices described here generally include an actuation mechanism within the housing that deploys the conduit from the housing and enables the delivery of drug from the device into the intraocular space. In other variations, the conduit is deployed by an actuation mechanism contained within a separate cartridge that can be removably attached to the device housing, e.g., using snap-fit or other interlocking elements. The actuation mechanisms may have any suitable configuration, so long as they provide for accurate, atraumatic, and controlled delivery of drug into the intraocular space. For example, the actuation mechanisms may deliver a drug or formulation into the eye by way of intraocular injection at a rate ranging from about 1 µl/sec to about 1 ml/sec, from about 5 µl/sec to about 200 µl/sec, or from about 10 µl/sec to about 100 µl/sec. The actuation mechanisms may generally provide a force of needle deployment that is strong enough to penetrate the eye wall comprising the conjunctiva, sclera and the pars plana region of the ciliary body, but less than that causing damage to the intraocular structures due to high velocity impact. This force depends on several physical factors, including but not limited to, the needle gauge utilized, the speed/rate of needle deployment at the point of contact between the needle tip and the eye wall which in turn determines the impact force. An exemplary range of force that may be generated by the actuation mechanisms is about 0.1 N (Newton) to about 1.0 N (Newton). The velocity of needle deployment may also range between about 0.05 seconds and about 5 seconds.

**[0152]** In some variations, the actuation mechanism is a single-spring mechanism. In other variations, the actuation mechanism is a two-spring mechanism. In further variations, the actuation mechanism is pneumatic, e.g., employing negative pressure such as vacuum, or a positive pressure driven mechanism. In further variations, the actuation mechanism is driven magnetically or electrically, e.g., by a piezo-electric or magnetic rail mechanism. These types of actuation mechanisms may be configured to allow independent control of the rate and force of drug injection (controlled, e.g., by the first spring member in the two-spring variation), and the rate and force of the dispensing member deployment (controlled, e.g., by the second spring member in the two-spring variation). Exemplary two-spring mechanisms are shown in FIGS. 26 and 27.

**[0153]** FIG. 28 also depicts an exemplary integrated intraocular drug delivery device with a two-spring actuation mechanism. In FIG. 28, the device (100) includes a housing (102)

having a proximal end (104) and a distal end (106). An ocular contact surface (108) is attached to the distal end (106). A measuring component (110) is attached to one side of the ocular contact surface (108). As further described below, a trigger (112) that is operatively coupled to the housing (102) works with the first spring (114) and the second spring (116) of the actuation mechanism to deploy pins (118) through openings (120) in the housing (102), to thereby deliver drug from the reservoir (122). First spring (114), second spring (116), pins (118), openings (120), and reservoir (122) are better shown in FIG. 29. Also in FIG. 29, a conduit, e.g., needle (124), is depicted within the housing in its first non-deployed state. Needle (124) is configured as being part of an assembly (125) such that movement of the assembly results in corresponding movement of the needle (124). A stop (115) is provided at the proximal end (127) of the assembly (125), which is connected to the distal end of the first spring (114) and the proximal end of the second spring (116). The springs, as well as other components of the device may be connected via medical grade adhesives, friction or snap fit, etc.

**[0154]** In FIG. 30, the second spring (116) is operatively connected to a plunger (132) by friction fit within a compartment (134) of the plunger (132). In the pre-activated state, as shown in FIG. 29, the plunger (132) and second spring (116) are held in place by pins (118). The pins (118) are removably engaged to the plunger (132) at plunger groove (138), and lock the plunger (132) in place via friction fit against the plunger groove (138) and housing (102).

**[0155]** Activation of the first spring (114) of the actuation mechanism by activating the trigger deploys the needle (124) into the intraocular space, i.e., it moves the needle (124) from its first non-deployed state (FIG. 29) to its second deployed state (FIG. 30). Referring to FIGS. 30 and 31A-31C, activation of the first spring (114) occurs by depression of trigger (112) by, e.g., one or two fingers, which also depresses buttons (126). As shown in FIGS. 31A and 31B, buttons (126) are configured with a button groove (128) that allows the buttons (126) to align with channels (130) in the housing (102). Once aligned with the channels (130), the buttons (126) may be slidingly advanced along the channels (130). The rate of movement along the channels (130) may be controlled manually by the user, automatically controlled by the force of spring expansion, or a combination of both. This movement of the buttons (126) allows expansion of the first spring (114) against stop (115) so that the needle assembly (125) and needle (124) can be deployed. The channels in the housing may have any suitable configuration. For example, as shown in FIG. 31C, the channels (130) may be

spiral cut within the housing to allow rotation or a corkscrew type movement of the needle upon advancement, which may facilitate needle penetration through the eye wall.

**[0156]** Activation of the first spring (114) will typically result in activation of the second spring (116) to deliver drug out of the device and into the intraocular space. For example, as shown in FIG. 30, the expansion force of first spring (114) against stop (115) that is also connected to the proximal end of the second spring (116) works to expand the second spring (116) so that the assembly (125) is advanced within the housing (102). As illustrated in FIGS. 32A-32C, when the pins (118) that are removably engaged to plunger (132) reach openings (120), they are deployed out through the openings (120). Expulsion of the pins (118) from the device, then allows free expansion of the second spring (116) against plunger (132), to thereby push drug residing with reservoir (122) out of the device. The openings (120) may be covered by a membrane or seal (140) that can be penetrated by the pins (118) to give a visual indication that the drug has been delivered.

**[0157]** A two-spring actuation mechanism, as shown in FIGS. 41A-41B may also be used. Referring to FIG. 41A, integrated device (600) includes an actuation mechanism comprising a first spring (602) and a second spring (604). In use, when trigger (606), e.g., a lever, is depressed, first spring (602) is released to advance shaft (608) in the direction of the arrow, which in turn advances needle (610) out of the tip of the device (600). Continued advancement of the shaft (608) advances the injection sleeve (612) and top seal (614) so that drug within reservoir (616) may be delivered through needle (610). Referring to FIG. 41 B, once the drug has been injected, tabs (618) removably engage housing openings (620) to thereby release second spring (604), which then moves shaft (608) backward to retract needle (610) (not shown).

**[0158]** In some variations, a single-spring actuation mechanism is employed, as shown in FIGS. 36 and 37. When a single spring is used, the actuation mechanism is configured much like the two-spring mechanism described above except that the second spring is removed. Thus, in its pre-activated state, as shown in FIG. 36, a device (300) with a single spring (302) may activate the single spring (302) by depression of trigger (304) by, e.g., one or two fingers, which also depresses buttons (306). The buttons (306) are configured with a button groove (308) that allows the buttons (306) to align with channels (not shown) in the housing (310). Once aligned with the channels, the buttons (306) may be slidingly advanced along the channels. This movement of the buttons (306) allows expansion of the spring (302)

against plunger (312) so that the needle assembly (314) and needle (316) can be deployed. When the pins (318) that are removably engaged to plunger (312) reach openings (320) within the housing (310), they are deployed out through the openings (320). Expulsion of the pins (318) from the device, then allows further expansion of the spring (302) against plunger (312), to thereby push drug residing with reservoir (322) out of the device. Although not shown here, the openings (320) may be covered by a membrane or seal that can be penetrated by the pins (318) to give a visual indication that the drug has been delivered.

**[0159]** A pneumatic actuation mechanism may also be employed. In one variation, as depicted in FIGS. 34 and 35A and 35B, the pneumatic actuation mechanism includes a plunger, pins, and housing openings in the same fashion as described for the single- and two-spring mechanisms. However, instead of using a spring to deploy the needle assembly and plunger, a piston is used to slidingly advance the needle assembly within the housing. For example, in FIG. 34, a device with a pneumatic actuation mechanism (200) includes a piston (202) and trigger (204). The piston (202) is used to compress air into the housing (206) of the device (202). If desired, the amount of compressed air the piston includes in the device may be controlled by a dial or other mechanism (not shown). The proximal end of the housing may also be configured, e.g., with a flange, crimps, or other containment structure, that allows translational movement of the piston (202) into the housing but not out of the housing. Upon depression of a trigger (208), a pair of locking pins (210) are also depressed to thereby allow the compressed air generated by the piston (202) to push the needle assembly (212) forward. This advancement of the needle assembly (212) deploys the needle (214) out of the device (FIG. 35B). As previously stated, pins (216) similar to those above that lock the plunger (218) in place are also provided. Upon their expulsion from the device out of openings (220) in the housing (206) due to forward movement of the needle assembly (212), the compressed air further moves the plunger (218) forward to thereby push drug residing with reservoir (222) out of the device. Rotational pins (224) may also be included, which upon release by the sliding needle assembly (212) allow rotation of the needle assembly (212) with respect to the housing (206).

**[0160]** As previously stated, a trigger may be coupled to the housing and configured to activate the actuation mechanism. In one variation, the trigger is located on the side of the device housing proximate the device tip at the ocular interface surface (e.g., the distance between the trigger and device tip may range between 5 mm to 50 mm, between 10 mm to 25

mm, or between 15 mm to 20 mm), so that the trigger can be activated by a fingertip while the device is positioned over the desired ocular surface site with the fingers on the same hand. In another variation, the trigger is located on the side of the device housing at 90 degrees to the measuring component, so that when the ocular contact surface is placed on the eye surface perpendicular to the limbus, the trigger can be activated with the tip of the second or third finger of the same hand that positions the device on the ocular surface.

**[0161]** Some variations of the device may include a control lever for initiating plunger movement. In these instances, the control lever may actuate the plunger in a mechanical manner, e.g., by spring-actuation, similar to that described above. In other variations, actuation of the plunger may occur through a combination of mechanical and manual features. For example, the initiation of plunger movement may be aided by a manual force applied onto the control lever, while a spring-actuated mechanism for generating a mechanical force is also employed to move the plunger forward inside the device barrel to inject drug. In instances where the control lever is connected to the plunger, the initiation of plunger movement and drug injection is controlled by the manual component, whereas the rate of fluid injection is controlled by the mechanical force. Here a reduced manual force may be applied to the plunger due to its combination with a co-directional mechanical force, thus facilitating the stability of device positioning on the ocular surface at a precise injection site.

**[0162]** The control lever may be placed between 10 mm and 50 mm from the tip of the device that interfaces with the eye surface, or between 20 mm and 40 mm from the tip of the device. Positioning of the control lever in this manner may enable atraumatic and precise operation of the device with one hand.

**[0163]** As illustrated in FIGS. 43A-43D, exemplary integrated device (700) includes a housing (702), a dynamic sleeve (704) slidable thereon, an ocular contact surface (706), a plunger (708), and a control lever (710) for manually actuating the plunger (708) to inject drug through needle (712). An expanded sectional view of the ocular contact surface (706), dynamic sleeve (706), plunger (708), and needle (712) shown in FIG. 43 A is shown in FIG. 43B. In use, after placing the ocular contact surface (706) on the eye, the applied pressure may automatically slide the dynamic sleeve (704) back (in the direction of the arrow) to expose the needle and allow needle penetration through the eye wall. The control lever (710) may then be slidably advanced manually (in the direction of the arrow in FIG. 43C) to

advance plunger (708). When injection of the drug through the needle (712) is complete, the dynamic sleeve (704) may be slidably advanced manually to cover the needle, as shown in FIG. 43D.

**[0164]** The dynamic sleeve may be slidably advanced or retracted manually by a fine mobility control mechanism, also referred to as a mobility control mechanism. In these instances, the dynamic sleeve may comprise a high-traction surface located on the outer surface of the sleeve, which may aid movement of the sleeve with a fingertip. In one variation, the high-traction surface may be engraved or contain markings with a serrated pattern. In other variations, as shown in FIG. 45A, a platform or pad (e.g., a fingertip pad) (900) may be attached to the outer surface of the sleeve (902) to help manually advance or retract the sleeve. The platform or pad may also include a high-traction surface (904), the perspective, side, and top views of which are illustrated in FIGS. 45B, 45C, and 45D, respectively. Platform or pad (900) will typically include a base (912) for attachment to the sleeve (902). Base (912) may be of any suitable configuration. For example, the base of the platform or pad may be configured as a cylinder (FIG. 45H) or with a narrowed portion (portion of lesser diameter), such as a dumbbell or apple core shape (FIG. 45I).

**[0165]** Some variations of the devices described herein include a grip having a retraction slot or channel that works in combination with the dynamic resistance component to inject drug into the eye. Referring to FIG. 45 A, grip (906) may be a component coupled (usually fixedly attached) to the device housing (908) at the proximal end (912) of the sleeve (902). The grip (906) may be configured to include a retraction slot (910) in its wall. In use, when the sleeve (902) is retracted, as shown by the direction of the arrow in FIG. 45J, the base (912) of the pad or platform is moved into the slot (910). The retraction slot (910) may be configured as a channel of uniform width (FIG. 45F), or as a channel with a keyhole-type configuration, e.g., having a narrowed portion (FIG. 45G) or enlarged portion (FIG. 45E) at the slot proximal or distal end. The retraction slot may provide sensory feedback, e.g., when the endpoint of retraction is reached. The configuration of the base of the platform or pad may be chosen so that it provides a friction fit with the slot. For example, when the slot has a narrowed portion, the base may also have a narrowed portion.

**[0166]** When grips are employed, the devices may also include a locking mechanism. In one variation, when the end point of the sleeve retraction and needle exposure/deployment is reached, the wide portion of the sleeve slot is aligned with the wide portion of a grip slot and

with an opening in the housing and an opening in the plunger shaft, allowing the platform base to be inserted into the plunger shaft to lock it relative to the platform that become an actuation lever for manual drug injection. The narrow part of the base enters the narrow part of the sleeve slot, which unlocks the platform relative to the sleeve allowing its movement towards device tip. In another variation, when the platform base reaches the end point of the retraction slot, it may be depressed into an opening in the plunger shaft and becomes a locking pin to connect the platform and the plunger. When it is depressed, its narrow portion enters the keyhole-shaped slot in the sleeve, and becomes movable within the slot moving towards the tip of the sleeve (unlocks the platform base and sleeve).

**[0167]** The mobility control mechanism may be beneficial when the user desires to control the amount of pressure exerted by the device tip on the eye surface in order to deploy the needle during its intraocular penetration. With a mobility control mechanism, the user may use a fingertip to either reduce or increase counter-forces that regulate the sleeve movement and needle exposure.

**[0168]** For example, if the user exerts the pulling force onto the said high-traction surface (that is pulling the high-traction surface of the sleeve away from the device tip), this movement may facilitate needle exposure and reduce the amount of pressure force (down to 0 Newton) needed to be applied to the eye wall in order to slide the sleeve back and expose the needle. In another variation, if the user exerts a pushing force (that is pushing the high-traction surface of the sleeve towards the device tip), this movement may counteract and impedes needle exposure, which may allow the device tip to apply increased pressure to the eye wall prior to the initiation of sleeve movement and needle exposure.

**[0169]** In use, the platform or pad may be slid with a second or third finger. Again, this allows the injector to manually modulate the sleeve resistance and movement along the device tip. For example, by pushing the pad and thus the sleeve forward with a fingertip, the injector provides some resistance at the beginning of the procedure when the device tip is being positioned on the eye surface (and the needle needs to remain completely covered). Then the injector would release his/her fingertip from the sleeve pad to enable needle deployment and its transscleral penetration. Some variations of the device may also include a step or a ring-shaped ridge at the end of the sleeve path, so that after the sleeve is pulled back past this step, it would automatically trigger spring-actuated plunger movement. The

fingertip pad could be used to pull the sleeve back past the said step at the end of needle deployment in order to actuate the plunger movement and drug injection.

**[0170]** When a platform or pad is employed, it may reduce the amount of pressure the device exerts on the eyeball before the sleeve begins to move to expose the needle, and thus, allow customization of the amount of applied pressure from patient to patient.

**[0171]** In another aspect, the dynamic sleeve may provide gradual needle exposure as it penetrates through the eye wall so that the needle is exposed 1 mm or less when it meets most resistance at the eye surface. Here the rest of the needle is located inside the sleeve with at least its most distal unexposed point or a longer segment being protected inside the narrow exit orifice or canal. Such sleeve design may minimize the risk of needle bending compared to the conventional syringe with a long exposed needle. This design may enable the utilization of smaller a gauge needle without increased risk of it being bent as it penetrated through the eye wall. The smaller needle gauge may render it more comfortable and less traumatic during its intraocular penetration.

II. METHODS

**[0172]** Methods for using the integrated intraocular drug delivery devices are also described herein. In general, the methods include the steps of positioning an ocular contact surface of the device on the surface of an eye, applying pressure against the surface of the eye at a target injection site using the ocular contact surface, and delivering an active agent from the reservoir of the device into the eye by activating an actuation mechanism. The steps of positioning, applying, and delivering are typically completed with one hand.

**[0173]** The application of pressure against the surface of the eye using the ocular contact surface may also be used to generate an intraocular pressure ranging between 15 mm Hg to 120 mm Hg, between 20 mm Hg to 90 mm Hg, or between 25 mm Hg to 60 mm Hg. As previously stated, the generation of intraocular pressure before deployment of the dispensing member (conduit) may reduce scleral pliability, which in turn may facilitate the penetration of the conduit through the sclera, decrease any unpleasant sensation on the eye surface during an injection procedure, and/or prevent backlash of the device. Intraocular pressure control may be generated or maintained manually or automatically using pressure relief valves, pressure sensors, pressure accumulators, pressure sensors, or components such as slidable caps having locking mechanisms and/or ridges as previously described.

**[0174]** Use of the devices according to the described methods may reduce pain associated with needle penetration through the various covers of the eye wall such as the conjunctiva that is richly innervated with pain nerve endings. The anesthetic effect at the injection site during an intraocular injection procedure may be provided by applying mechanical pressure on the conjunctiva and the eye wall over the injection site before and/or during the needle injection. The application of mechanical pressure to the eye wall may also transiently increase intraocular pressure and increase firmness of the eye wall (and decrease its elasticity), thereby facilitating needle penetration through the sclera. Furthermore, the application of mechanical pressure to the eye wall may displace intraocular fluid within the eye to create a potential space for the drug injected by the device.

**[0175]** The devices may be used to treat any suitable ocular condition. Exemplary ocular conditions include without limitation, any type of retinal or macular edema as well as diseases associated with retinal or macular edema, e.g., age-related macular degeneration, diabetic macular edema, cystoid macular edema, and post-operative macular edema; retinal vascular occlusive diseases such as CRVO (central retinal vein occlusion), BRVO (branch retinal vein occlusion), CRAO (central retinal artery occlusion), BRAO (branch retinal artery occlusion), and ROP (retinopathy of prematurity), neovascular glaucoma; uveitis; central serous chorioretinopathy; and diabetic retinopathy.

**[0176]** When dexamethasone sodium phosphate solution is used to treat an ocular condition, the dose of dexamethasone sodium phosphate that may be administered into the eye by each individual injection device may range between about 0.05 mg and about 5.0 mg, between about 0.1 mg and about 2.0 mg, or between about 0.4 mg and about 1.2 mg.

**[0177]** In some variations, a topical anesthetic agent is applied on the ocular surface before placement of the device on the eye. Any suitable topical anesthetic agent may be used. Exemplary topical anesthetic agents include without limitation, lidocaine, proparacaine, prilocaine, tetracaine, betacaine, benzocaine, bupivacaine, ELA-Max®, EMLA® (eutectic mixture of local anesthetics), and combinations thereof. In one variation, the topical anesthetic agent comprises lidocaine. When lidocaine is used, it may be provided in a concentration raging from about 1% to about 10%, from about 1.5% to about 7%, or from about 2% to about 5%. In another variation, the topical anesthetic agent is mixed with phenylephrine or another agent that potentiates or/and prolongs the anesthetic effect of the

pharmaceutical formulation. The topical anesthetic agent may be provided in any suitable form. For example, it may be provided as a solution, gel, ointment, etc.

**[0178]** An antiseptic agent may also be applied on the ocular surface before placement of the device on the eye. Examples of suitable antiseptic agents include, but are not limited to, iodine, povidone-iodine (betadine®), chlorhexidine, soap, antibiotics, salts and derivatives thereof, and combinations thereof. The antiseptic agent may or may not be applied in combination with a topical anesthetic agent. When the antiseptic comprises povidone-iodine (Betadine®), the concentration of povidone-iodine may range from about 1% to about 10%, from about 2.5% to about 7.5%, or from about 4% to about 6%.

**[0179]** During the drug delivery process, the devices described here may be configured so that the injection needle enters the eye at the right angle that is perpendicular to the eye wall (sclera). In other instances, the device may be configured so that the injection needle enters through the cornea into the anterior chamber of the eye parallel to the iris plane.

III. SYSTEMS AND KITS

**[0180]** Systems and kits that include the intraocular drug delivery devices are also described herein. The kits may include one or more integrated drug delivery devices. Such devices may be preloaded with an active agent. When a plurality of preloaded devices are included, they may be separately packaged and contain the same active agent or different active agents, and contain the same dose or different doses of the active agent.

**[0181]** The systems and kits may also include one or more separately packaged devices that are to be manually loaded. If the devices are to be manually loaded prior to use, then one or more separately packaged active agents may be incorporated into the kit. Similar to the preloaded device system or kit, the separately packaged active agents in the systems and kits here may be the same or different, and the dose provided by each separately packaged active agent may be the same or different.

**[0182]** Of course, the systems and kits may include any combination of preloaded devices, devices for manual loading, and active agents. It should also be understood that instructions for use of the devices will also be included. In some variations, one or more separately packaged measuring components may be provided in the systems and kits for removable

attachment to the devices. Topical anesthetic agents and/or antiseptic agents may also be included.

IV. EXAMPLES

**[0183]** The following example serves to more fully describe the manner of using the above-described intraocular injection devices. It is understood that this example in no way serves to limit the scope of the invention, but rather is presented for illustrative purposes.

Example 1: Resistance Force Generated By the Dynamic Sleeve

**[0184]** An intraocular injection device comprising a 30-gauge needle covered by a dynamic sleeve (a bi-tapered design with each end of the sleeve tapered) was fixed onto an Imada tensile testing bed and moved against an Imada 10 N force gauge at a rate of 10 mm/minute. The resistance force was measured while the sleeve was pushed back to expose the needle simulating the movement of the sleeve in practice. This produced a "U"-shaped force plotted against the sleeve displacement curve, as shown in FIG. 46. The resistance force at the beginning and the end of sleeve movement path was greater than that in the middle of the path. In FIG. 46, the illustrated range of resistance force generated may be between zero Newton and about 2 Newton or between about 0.1 Newton and about 1.0 Newton.

**[0185]** In one instance, the resistance force at the beginning of the sleeve path equaled the force required for the 30- or 31-gauge needle to penetrate through the human sclera (e.g., between 0.2 Newton and 0.5 Newton). When a using a higher-resistance sleeve was employed, the resistance force at the beginning of the sleeve path was greater than the force required for the 30- or 31-gauge needle to penetrate through the human sclera (e.g., over 1 Newton). However, the force was low enough to be comfortable for the patient and avoid potential damage to the eye (e.g., to avoid increase in intra-ocular pressure over 60 mmHg). In the middle portion of the sleeve movement path, the force approached zero Newton.

CLAIMS

1. An integrated device for intraocular drug delivery comprising:

a housing sized and shaped for manipulation with one hand, the housing having a proximal end and a distal end;

an ocular contact surface at the housing distal end;

a measuring component;

a conduit at least partially within the housing, the conduit having a proximal end, a distal end, and a lumen extending therethrough;

an actuation mechanism contained within the housing and operably connected to the conduit and a reservoir for holding an active agent;

a trigger coupled to the housing and configured to activate the actuation mechanism; and

a dynamic resistance component coupled to the housing.

2. The integrated device of claim 1, wherein the dynamic resistance component comprises a slidable element coupled to the housing.

3. The integrated device of claim 2, wherein the slidable element comprises a dynamic sleeve having a proximal end, a distal end, and an inner surface.

4. The integrated device of claim 3, wherein the proximal end and the distal end of the dynamic sleeve are tapered.

5. The integrated device of claim 4, wherein the tapered dynamic sleeve and the housing generate a force between 0 N and about 2 N.

6. The integrated device of claim 4, wherein the tapered dynamic sleeve and the housing generate a force between about 0.1 N and about 1 N.

7. The integrated device of claim 3, wherein the inner surface of the dynamic sleeve comprises one or more high-traction surfaces.

8. The integrated device of claim 7, wherein the housing comprises one or more high-traction surfaces.

9. The integrated device of claim 8, wherein the one or more high-traction surfaces of the dynamic sleeve and the housing generate a force between 0 N and about 2 N.

10. The integrated device of claim 8, wherein the one or more high-traction surfaces of the dynamic sleeve and the housing generate a force between about 0.1 N and about 1.0 N.

11. The integrated device of claim 3, wherein the dynamic sleeve further comprises a fine sleeve mobility control component.

12. The integrated device of claim 1, wherein the ocular contact surface comprises a ring, a flange, or a combination thereof.

13. The integrated device of claim 12, wherein the ocular contact surface comprises a ring.

14. The integrated device of claim 13, wherein the ring has a diameter between about 0.3 mm and about 8 mm.

15. The integrated device of claim 1, wherein the ocular contact surface is flat, convex, or concave.

16. The integrated device of claim 1, wherein the ocular contact surface comprises one or more traction elements.

17. The integrated device of claim 1, wherein the ocular contact surface comprises an adhesive component.

18. The integrated device of claim 17, wherein the adhesive component comprises a suction mechanism.

19. The integrated device of claim 1, wherein the ocular contact surface comprises a material selected from the group consisting of nylon fiber, cotton fiber, hydrogel, spongiform material,

styrofoam, other foams, silicone, plastic, polypropylene, polyethylene, polytetrafluoroethylene, and combinations thereof.

20. The integrated device of claim 1, wherein the actuation mechanism comprises a manual actuation mechanism.

21. The integrated device of claim 20, wherein the manual actuation mechanism comprises a control lever for slidable advancement of a plunger.

22. The integrated device of claim 1, wherein the actuation mechanism comprises an automated actuation mechanism.

23. The integrated device of claim 22, wherein the automated actuation mechanism comprises a spring-loaded actuation mechanism.

24. The integrated device of claim 23, wherein the spring-loaded actuation mechanism is configured to deliver the active agent into the intraocular space at a rate ranging from about 1 µl/sec to about 1 ml/sec.

25. The integrated device of claim 24, wherein the spring-loaded actuation mechanism delivers the active agent into the intraocular space at a rate ranging from about 10 µl/sec to about 100 µl/sec.

26. The integrated device of claim 23, wherein the spring-loaded actuation mechanism generates a force of about 0.1 N to about 1.0 N.

27. The integrated device of claim 23, wherein the spring-loaded actuation mechanism comprises a first spring and a second spring.

28. The integrated device of claim 27, wherein the second spring is configured to deploy a plunger and to control the rate of delivery of the active agent.

29. The integrated device of claim 27, wherein the first spring is configured to move the conduit from a first non-deployed state to a second deployed state and control the rate and force of deployment of the conduit.

30. The integrated device of claim 1, wherein the actuation mechanism is a partially automated actuation mechanism.

31. The integrated device of claim 30, wherein the partially automated actuation mechanism comprises a control lever for slidable advancement of a plunger.

32. The integrated device of claim 30, wherein the partially automated actuation mechanism comprises a spring-loaded actuation mechanism.

33. The integrated device of claim 32, wherein the spring-loaded actuation mechanism is configured to deliver the active agent into the intraocular space at a rate ranging from about 1 µl/sec to about 1 ml/sec.

34. The integrated device of claim 32, wherein the spring-loaded actuation mechanism delivers the active agent into the intraocular space at a rate ranging from about 10 µl/sec to about 100 µl/sec.

35. The integrated device of claim 32, wherein the spring-loaded actuation mechanism generates a force of about 0.1 N to about 1.0 N.

36. The integrated device of claim 32, wherein the spring-loaded actuation mechanism comprises a first spring and a second spring.

37. The integrated device of claim 36, wherein the second spring is configured to deploy a plunger and to control the rate of delivery of the active agent.

38. The integrated device of claim 36, wherein the first spring is configured to move the conduit from a first non-deployed state to a second deployed state and control the rate and force of deployment of the conduit.

39. The integrated device of claim 1, wherein the actuation mechanism is a pneumatic actuation mechanism.

40. The integrated device of claim 1, wherein the active agent is selected from the group consisting of steroidal anti-inflammatories, nonsteroidal anti-inflammatories, anti-infectives, anti-allergens, cholinergic antagonists and agonists, adrenergic antagonists and agonists, anti-glaucoma agents, neuroprotection agents, agents for cataract prevention or treatment, anti-proliferatives, anti-tumor agents, complement inhibitors, vitamins, growth factors, agents to inhibit growth factors, gene therapy vectors, chemotherapy agents, protein kinase inhibitors, small interfering RNAs, analogs, derivatives, and modifications thereof, and combinations thereof.

41. The integrated device of claim 1, wherein the active agent is selected from the group consisting of ranibizumab, bevacizumab, pegaptanib, dexamethasone, dexamethasone sodium phosphate, triamcinolone, triamcinolone acetonide, fluocinolone, taxol-like drugs, aflibercept, anecortave acetate, and limus family compounds.

42. The integrated device of claim 36, wherein the limus family compounds are selected from the group consisting of sirolimus, SDZ-RAD, tacrolimus, everolimus, pimecrolimus, zotarolimus, CCI-779, AP23841, and ABT-578, analogs, derivatives, conjugates, salts, and modifications thereof, and combinations thereof.

43. The integrated device of claim 1, wherein the reservoir is made from a cyclic olefin series resin.

44. The integrated device of claim 40, wherein the reservoir lacks silicone oil or one of its derivatives.

45. The integrated device of claim 1, wherein the measuring component is attached to the ocular contact surface.

46. The integrated device of claim 1, wherein the measuring component comprises one or more radially extending members.

47. The integrated device of claim 46, wherein the one or more radially extending members comprises a raised distal tip.

48. The integrated device of claim 46, wherein the one or more radially extending members is flexible.

49. The integrated device of claim 48, wherein the measuring component comprises a positional indicator component.

50. The integrated device of claim 1, wherein the reservoir is preloaded with the active agent.

51. The integrated device of claim 3, wherein one of the proximal end and distal end of the dynamic sleeve is tapered.

52. A method for intraocular drug delivery comprising:

positioning an ocular contact surface of an integrated device on the surface of an eye using a measuring component to determine the location of an injection site, the integrated device further comprising a housing, a dispensing member a dynamic resistance component, a reservoir for holding an active agent, and an actuation mechanism;

applying pressure against the surface of the eye at a target injection site using the dynamic resistance component; and

delivering an active agent from the reservoir into the eye by activating the actuation mechanism,

wherein the steps of positioning, applying, and delivering are completed with one hand.

53. The method of claim 52, wherein the injection site is between about 1 mm anterior to the limbus and about 6 mm posterior to the limbus.

54. The method of claim 52, wherein the injection site is between about 3 mm to about 4 mm posterior to the limbus.

55. The method of claim 52, wherein the active agent is preloaded in the reservoir.

56. The method of claim 52, wherein the active agent is loaded into the reservoir using a drug loading mechanism.

57. The method of claim 52, wherein the active agent is selected from the group consisting of steroidal anti-inflammatories, nonsteroidal anti-inflammatories, anti-infectives, anti-allergens, cholinergic antagonists and agonists, adrenergic antagonists and agonists, anti-glaucoma agents, neuroprotection agents, agents for cataract prevention or treatment, anti-proliferatives, anti-tumor agents, complement inhibitors, vitamins, growth factors, agents to inhibit growth factors, gene therapy vectors, chemotherapy agents, protein kinase inhibitors, small interfering RNAs, analogs, derivatives, conjugates, and modifications thereof, and combinations thereof.

58. The method of claim 52, wherein the active agent is selected from the group consisting of ranibizumab, bevacizumab, pegaptanib, dexamethasone, dexamethasone sodium phosphate, triamcinolone, triamcinolone acetonide, fluocinolone, taxol-like drugs, aflibercept, anecortave acetate, and limus family compounds.

59. The method of claim 58, wherein the limus family compounds are selected from the group consisting of sirolimus, SDZ-RAD, tacrolimus, everolimus, pimecrolimus, zotarolimus, CCI-779, AP23841, and ABT-578, analogs, derivatives, conjugates, salts, and modifications thereof, and combinations thereof.

60. The method of claim 52, wherein the active agent is used to treat an ocular condition selected from the group consisting of macular edema, cystoid macular edema, diabetic macular edema, post-operative macular edema, retinal edema, age-related macular degeneration, BRVO, CRVO, uveitis, and central serous chorioretinopathy.

61. The method of claim 52, wherein the actuation mechanism delivers the active agent into the intraocular space at a rate ranging from about 1 μl/sec to about 1 ml/sec.

62. The method of claim 52, wherein the actuation mechanism delivers the active agent into the intraocular space at a rate ranging from about 5 μl/sec to about 200 μl/sec.

63. The method of claim 52, wherein the actuation mechanism delivers the active agent into the intraocular space at a rate ranging from about 10 μl/sec to about 100 μl/sec.

64. The method of claim 52, wherein the actuation mechanism generates a force of about 0.1 N to about 1.0 N.

65. The method of claim 52, wherein the dynamic resistance component comprises a slidable element coupled to the housing of the integrated device.

66. The method of claim 65, wherein the slidable element comprises a dynamic sleeve having a tapered proximal end and a tapered distal end.

67. The method of claim 65, wherein the step of applying pressure against the surface of the eye retracts the slidable element to expose the dispensing member.

68. The method of claim 67, further comprising the step of manual actuation of a plunger to deliver the active agent.

69. The method of claim 52, wherein the step of applying pressure against the surface of the eye comprises slidable advancement of the dynamic resistance component.

70. The method of claim 69, wherein slidable advancement of the dynamic sleeve generates a force between itself and the housing ranging from 0 N to about 2 N.

71. The method of claim 69, wherein slidable advancement of the dynamic sleeve generates a force between itself and the housing ranging from about 0.1 N to about 1 N.

72. The method of claim 69, wherein the slidable advancement is manually adjustable.

73. The method of claim 69, wherein the slidable advancement is automatically adjustable.

74. The method of claim 52, wherein the dynamic resistance component comprises an ocular wall tension control mechanism.

75. An integrated device for intraocular drug delivery comprising:

a housing sized and shaped for manipulation with one hand, the housing having a proximal end and a distal end;

an ocular contact surface at the housing distal end;

a measuring component;

a conduit at least partially within the housing, the conduit having a proximal end, a distal end, and a lumen extending therethrough;

an actuation mechanism contained within the housing and operably connected to the conduit and a reservoir for holding an active agent;

a trigger coupled to the housing and configured to activate the actuation mechanism; and

an ocular wall tension control mechanism coupled to the housing.

76. The integrated device of claim 75, wherein the ocular wall tension control mechanism comprises a slidable cap having a locking mechanism.

77. The integrated device of claim 76, wherein the locking mechanism is a manually operated.

78. The integrated device of claim 76, wherein the locking mechanism is an automatically operated mechanism.

79. The integrated device of claim 76, wherein the locking mechanism comprises a locking pin.

80. The integrated device of claim 76, wherein the slidable cap comprises one or more high traction surfaces.

81. The integrated device of claim 80, wherein the one or more high traction surfaces comprise ridges on an inner surface of the slidable cap.

82. The integrated device of claim 75, wherein the ocular wall tension control mechanism comprises a pressure sensor.

83. The integrated device of claim 75, wherein the ocular wall tension control mechanism comprises a pressure accumulator.

84. A method for intraocular drug delivery comprising:

positioning an ocular contact surface of an integrated device on the surface of an eye using a measuring component to determine the location of an injection site, the integrated device further comprising a housing, a dispensing member an ocular wall tension control component, a reservoir for holding an active agent, and an actuation mechanism;

applying pressure against the surface of the eye at a target injection site using the ocular wall tension control component; and

delivering an active agent from the reservoir into the eye by activating the actuation mechanism,

wherein the steps of positioning, applying, and delivering are completed with one hand.

85. The method of claim 84, wherein the step of applying pressure against the surface of the eye comprises slidable advancement of the ocular wall tension control component.

86. The method of claim 85, wherein slidable advancement of the ocular wall tension control mechanism generates a force between itself and the housing ranging from 0 N to about 2 N.

87. The method of claim 85, wherein slidable advancement of the ocular wall tension control component generates a force between itself and the housing ranging from about 0.1 N to about 1 N.

88. An injection device for intraocular drug delivery comprising:

a housing sized and shaped for manipulation with one hand, the housing having a proximal end and a distal end;

an ocular contact surface at the housing distal end;

a conduit at least partially within the housing, the conduit having a proximal end, a distal end, and a lumen extending therethrough;

an actuation mechanism contained within the housing and operably connected to the conduit and a reservoir for holding an active agent;

a trigger coupled to the housing and configured to activate the actuation mechanism; and

a dynamic resistance component.

89. The injection device of claim 88, wherein the dynamic resistance component comprises a dynamic sleeve having a proximal end, a distal end, and an inner surface.

90. The injection device of claim 89, wherein the proximal end and the distal end of the dynamic sleeve are tapered.

91. The injection device of claim 89, wherein one of the proximal end and the distal end of the dynamic sleeve is tapered.

92. The injection device of claim 89, wherein the inner surface of the dynamic sleeve comprises ridges.

93. The injection device of claim 88, wherein the dynamic sleeve further comprises a fine sleeve mobility control component.

94. The injection device of claim 88, wherein the device further comprises a measuring component.

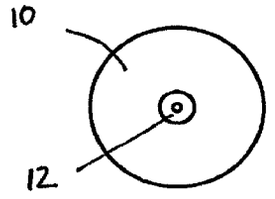



FIG. 1A

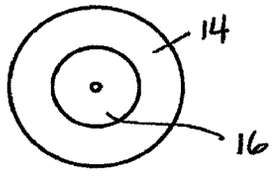



FIG. 1B

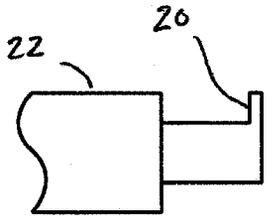



FIG. 2A

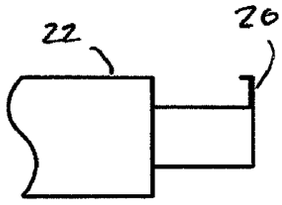



FIG. 2B

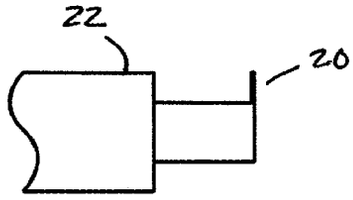
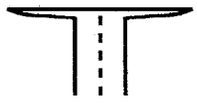



FIG. 2C

FIG. 3A1



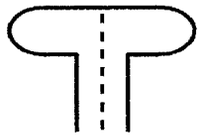
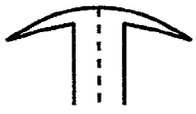


FIG. 3B1

FIG. 3A2



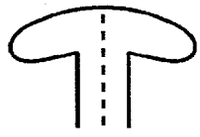


FIG. 3B2

FIG. 3A3

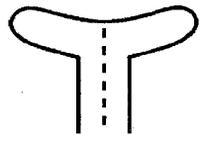


FIG. 3B3

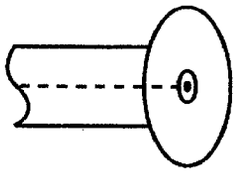


FIG. 4A

FIG. 4B1

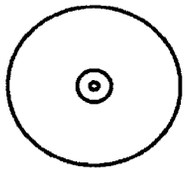


FIG. 4B2

FIG. 5A1

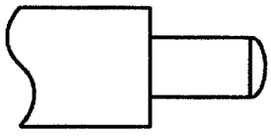


FIG. 5B1

FIG. 5A2

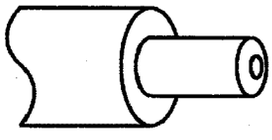
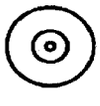


FIG. 5B2

FIG. 6A1



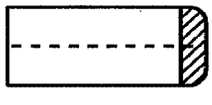
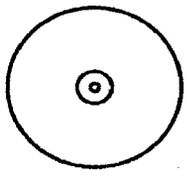


FIG. 6A2

FIG. 6B1



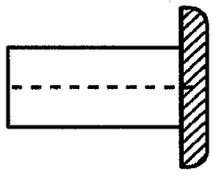


FIG. 6B2

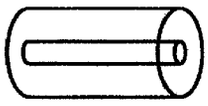
FIG. 7A1 

 FIG. 7A2

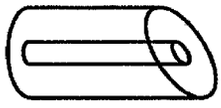
FIG. 7B1 

 FIG. 7B2

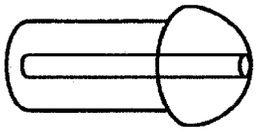
FIG. 7C1 

 FIG. 7C2

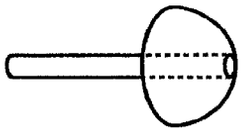
FIG. 7D 

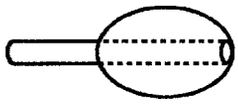
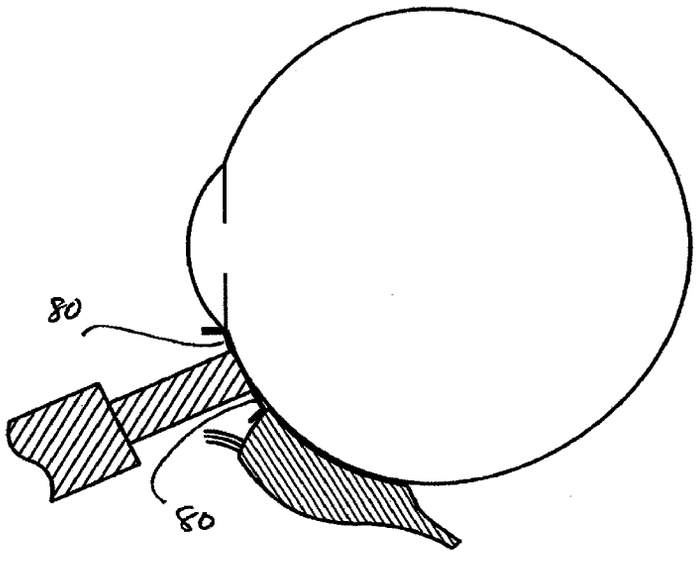
FIG. 7E 

FIG. 8



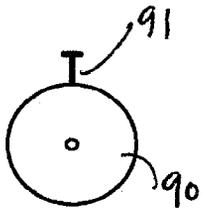



FIG. 9A

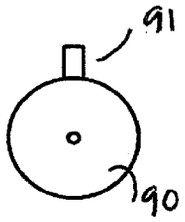



FIG. 9B

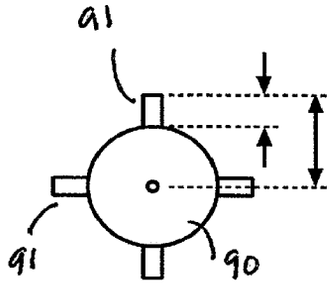



FIG. 9C

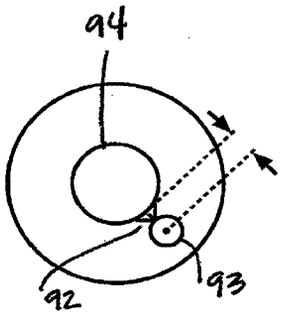



FIG. 10A

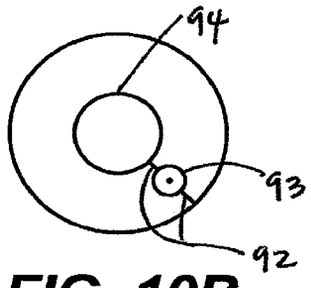



FIG. 10B

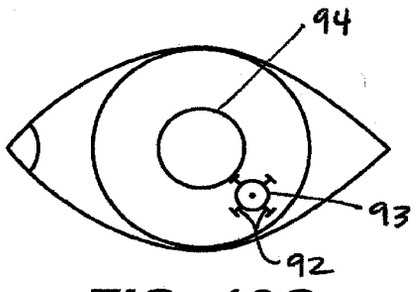



FIG. 10C

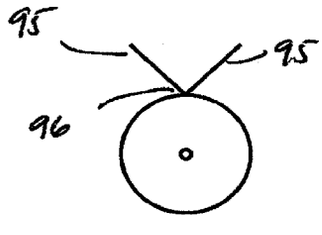



FIG. 11A

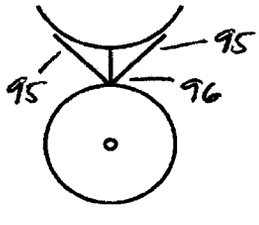



FIG. 11B

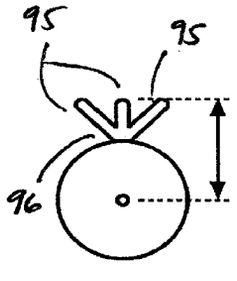



FIG. 11C

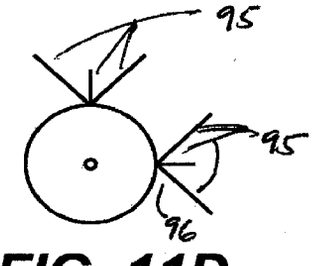



FIG. 11D

FIG. 12

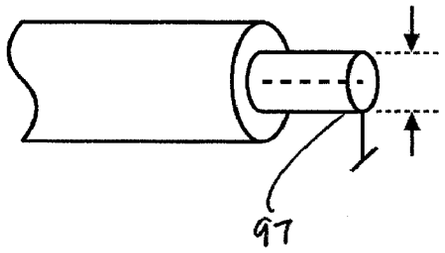



FIG. 13

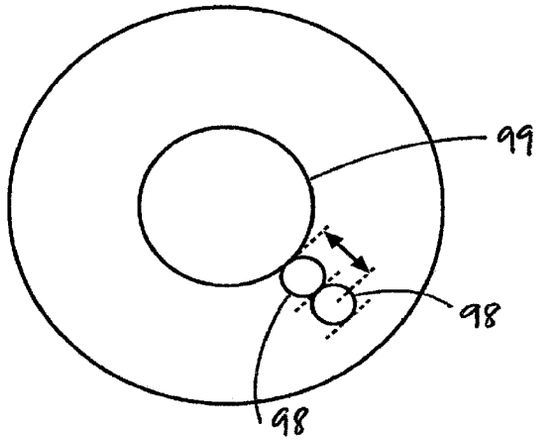



FIG. 14A

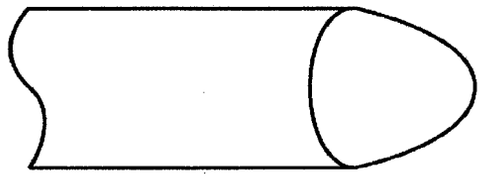


FIG. 14B

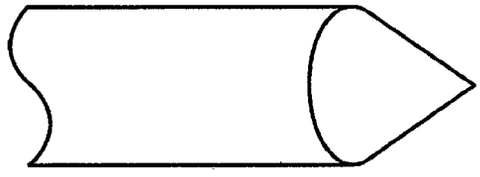


FIG. 14C

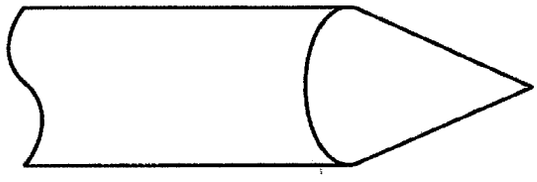


FIG. 15A1

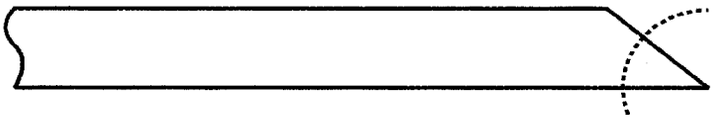


FIG. 15A2

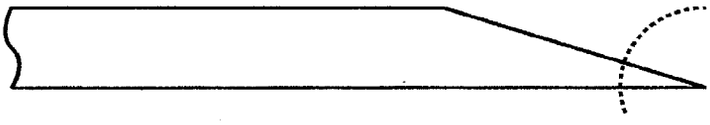


FIG. 16A

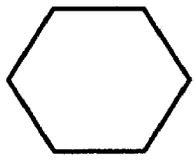


FIG. 16C

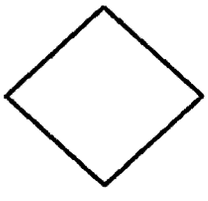


FIG. 16B

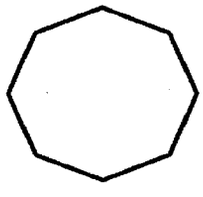
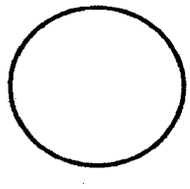


FIG. 16D



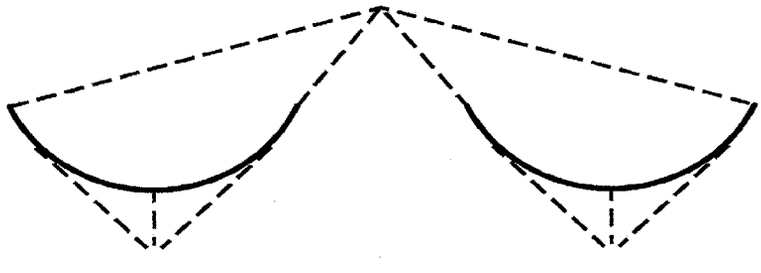


FIG. 17

FIG. 18A

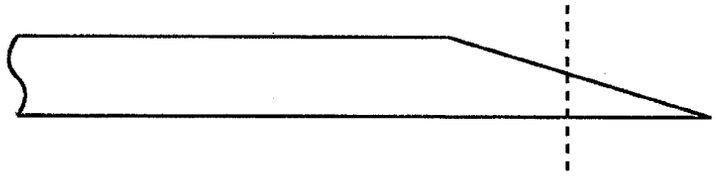


FIG. 18B

FIG. 18C

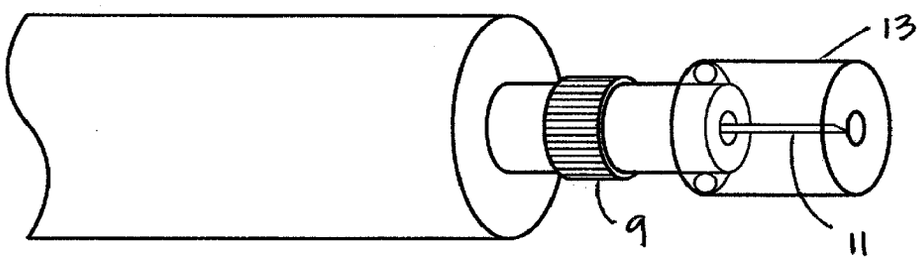



FIG. 19

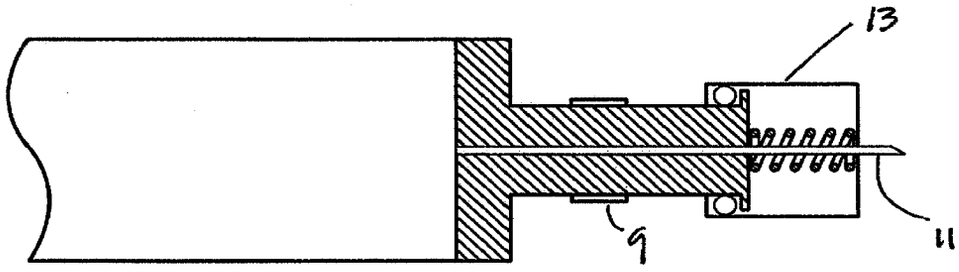



FIG. 20

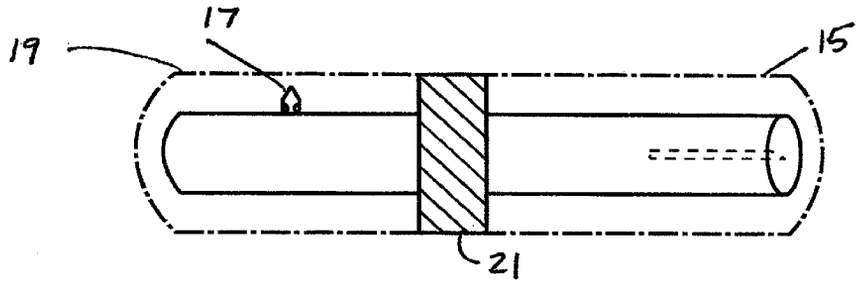



FIG. 21

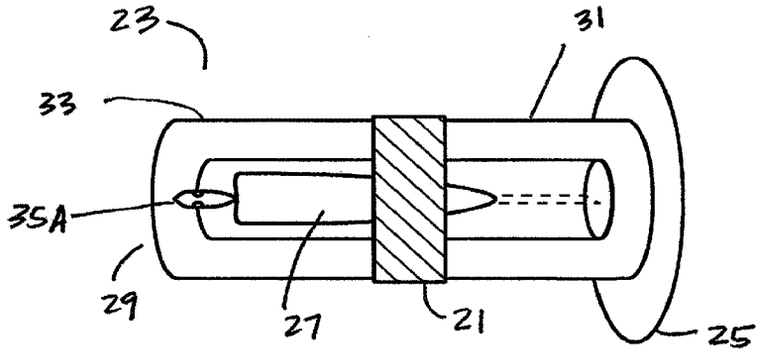



FIG. 22

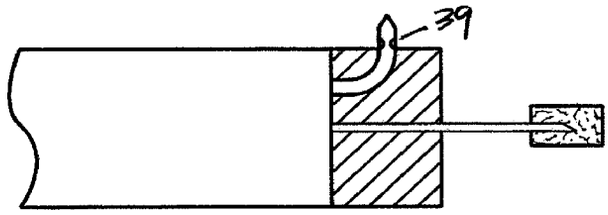



FIG. 23A

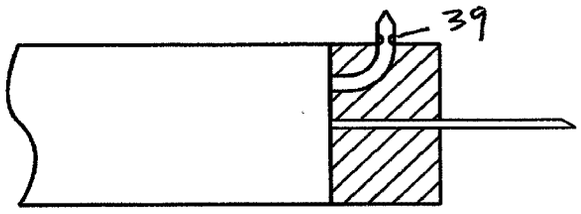



FIG. 23B

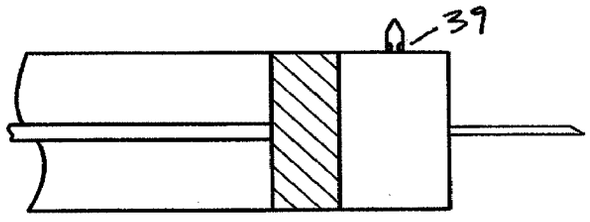



FIG. 23C

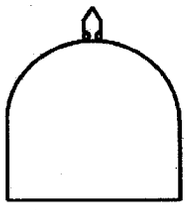


FIG. 24A

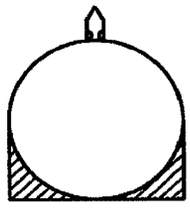


FIG. 24B

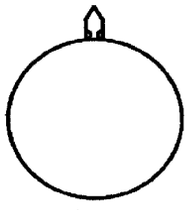


FIG. 24C

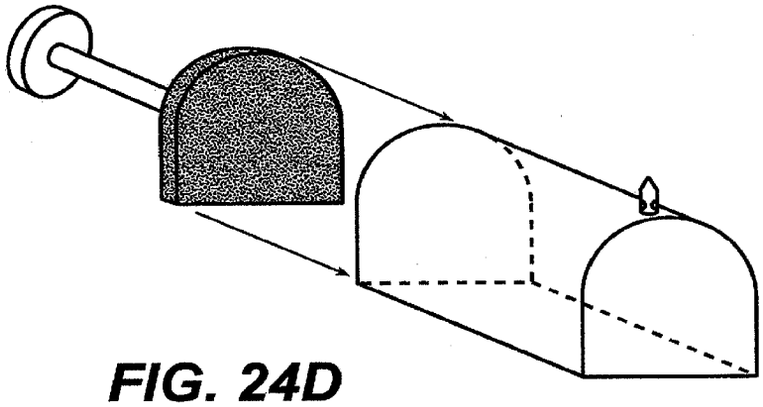


FIG. 24D

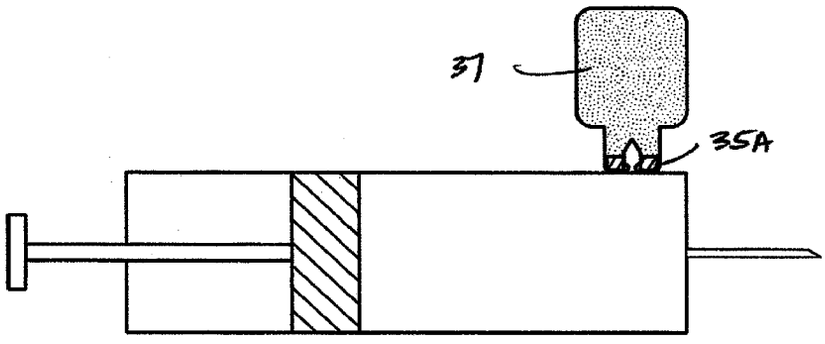



FIG. 25A

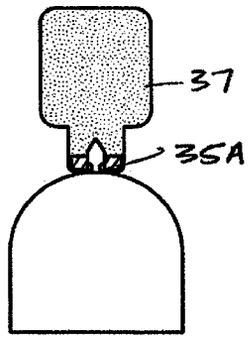



FIG. 25B

FIG. 26A

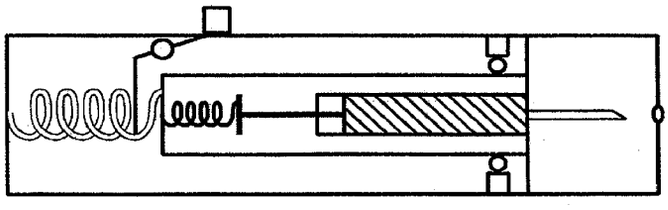


FIG. 26B

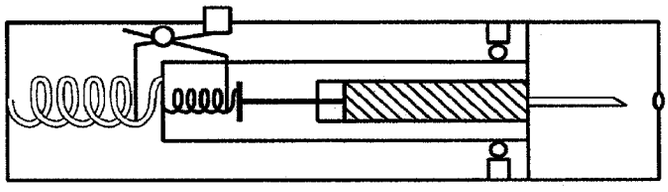


FIG. 26C

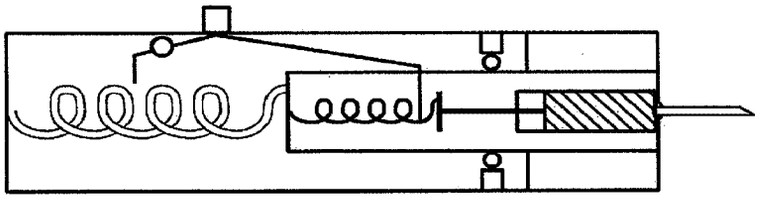
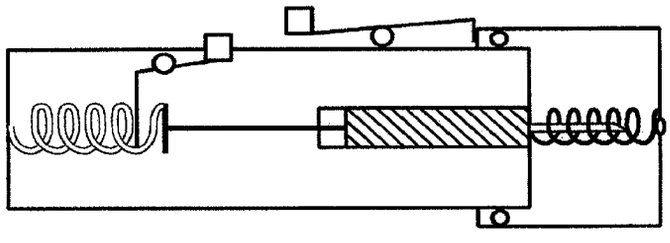


FIG. 27



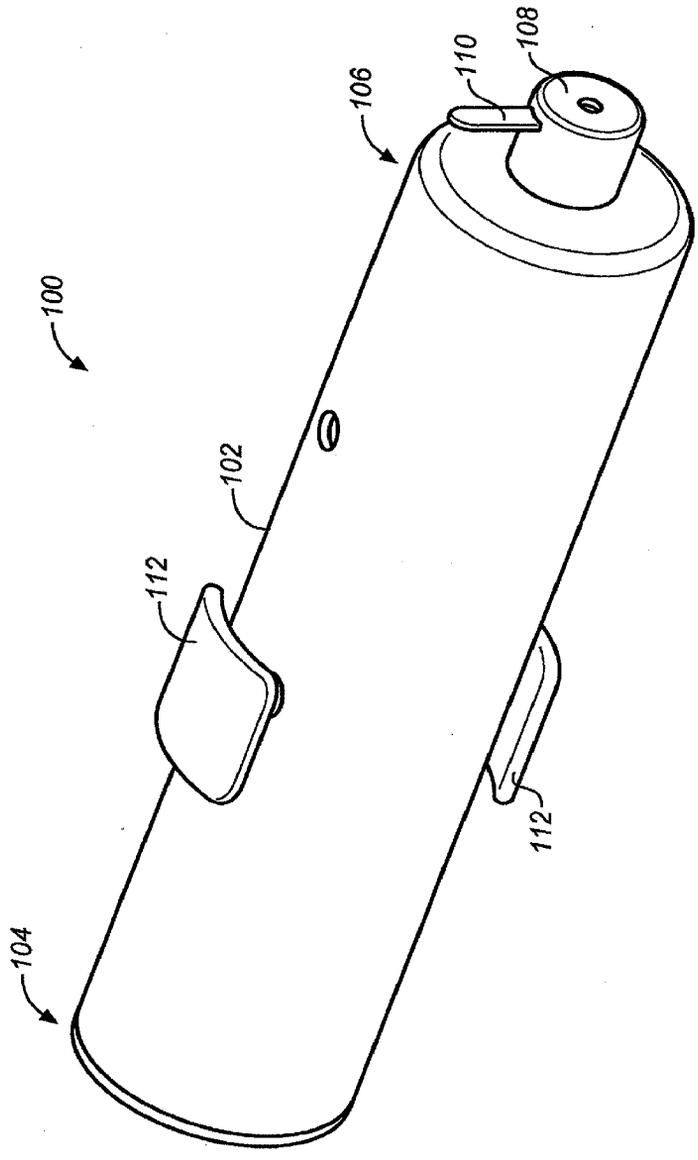



FIG. 28

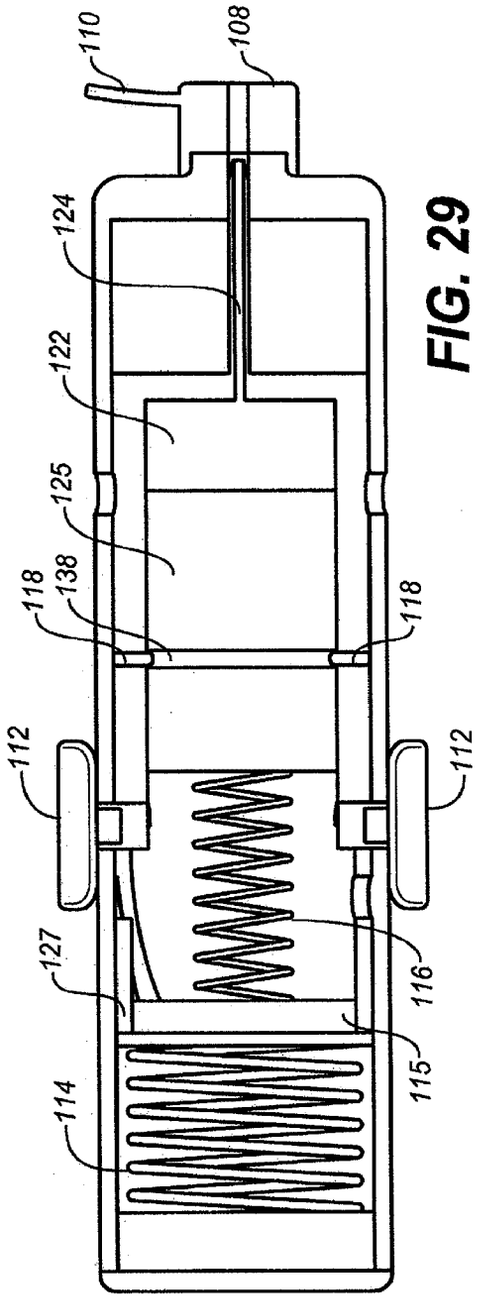



FIG. 29

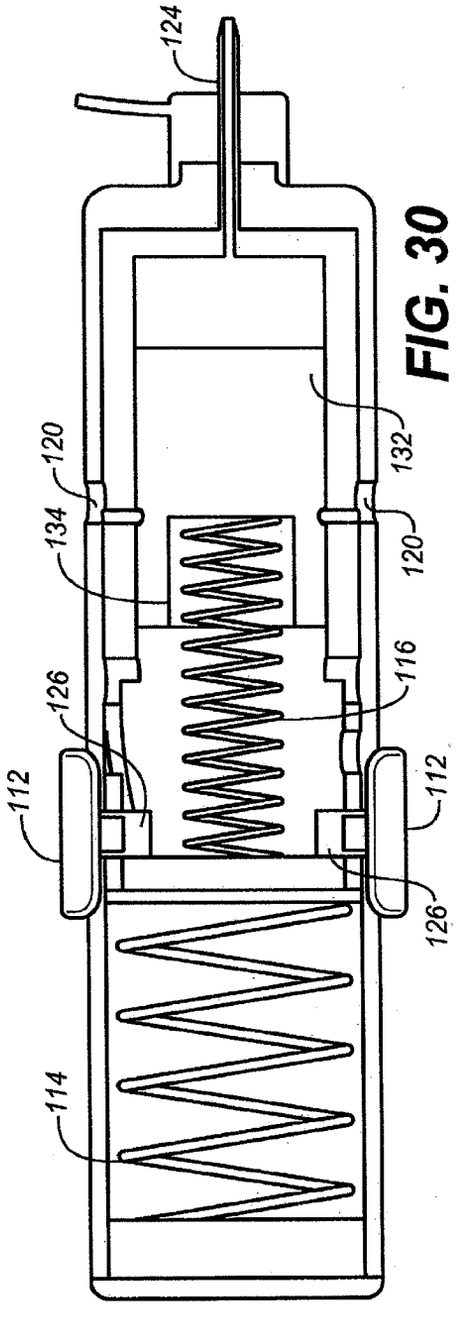



FIG. 30

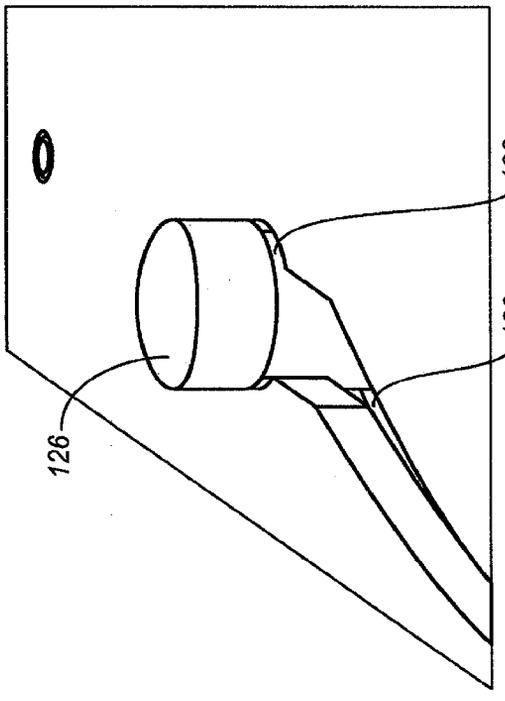



FIG. 31B

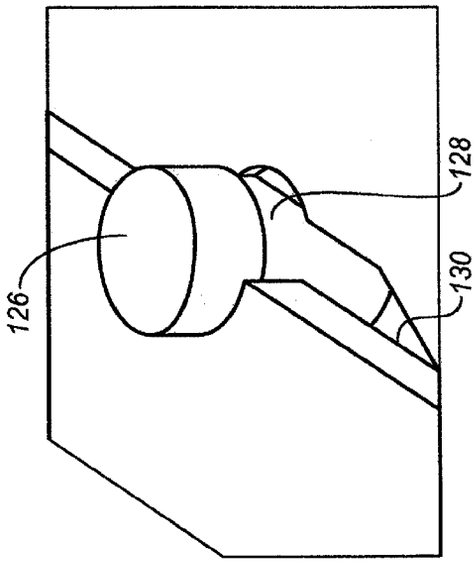



FIG. 31A

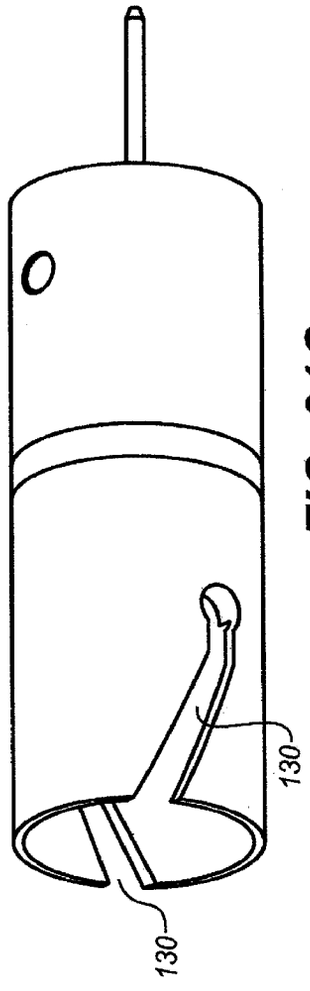



FIG. 31C

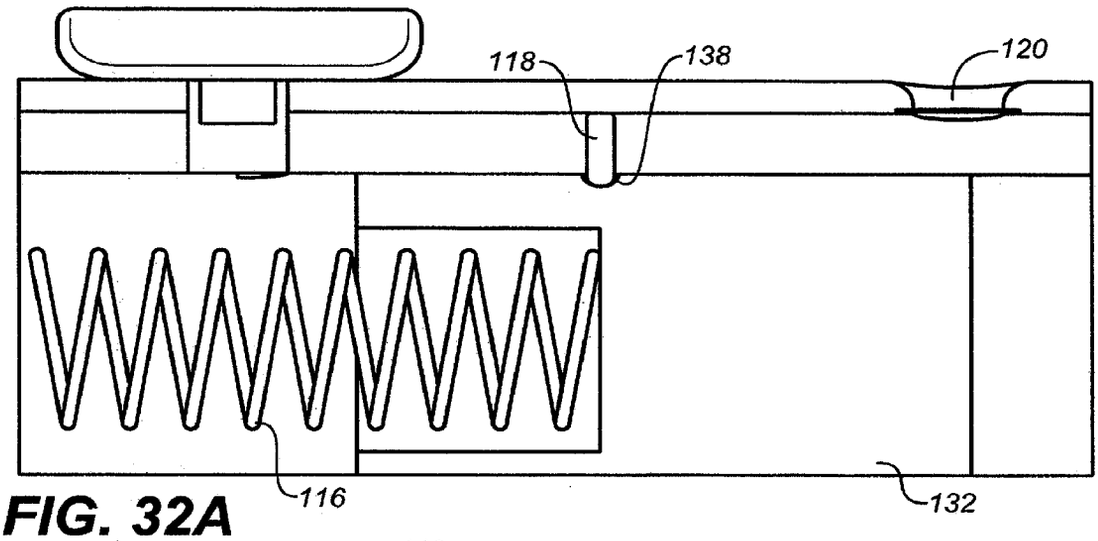



FIG. 32A

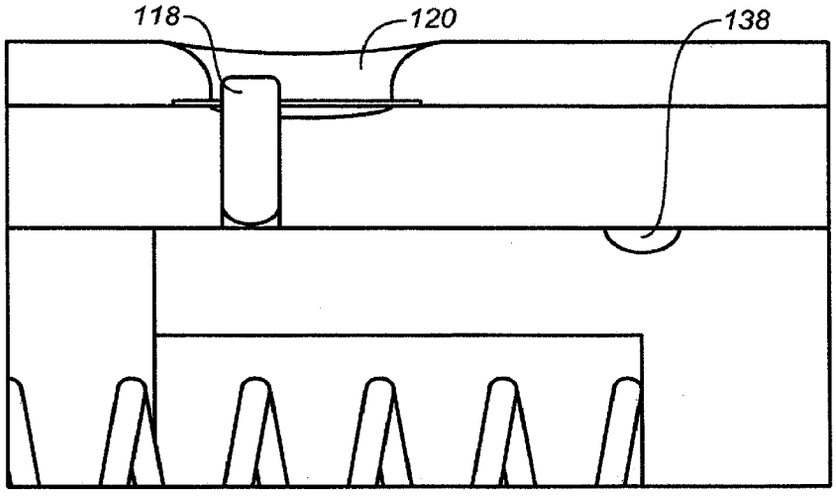



FIG. 32B

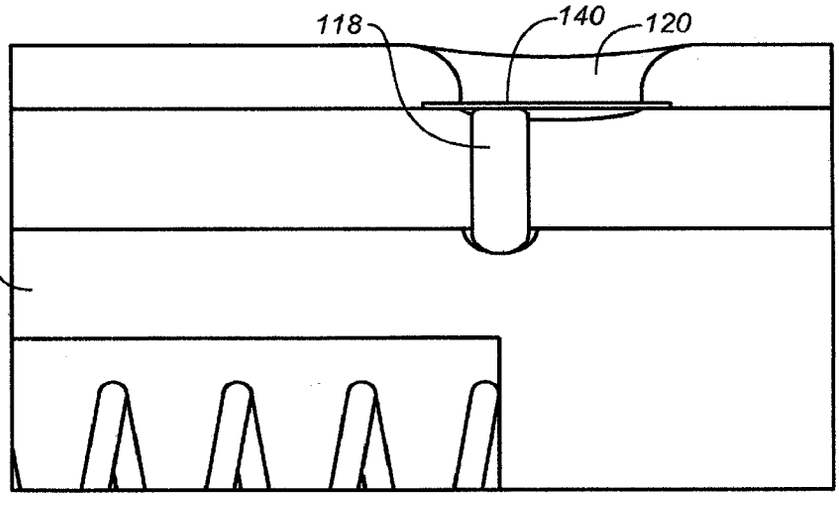



FIG. 32C

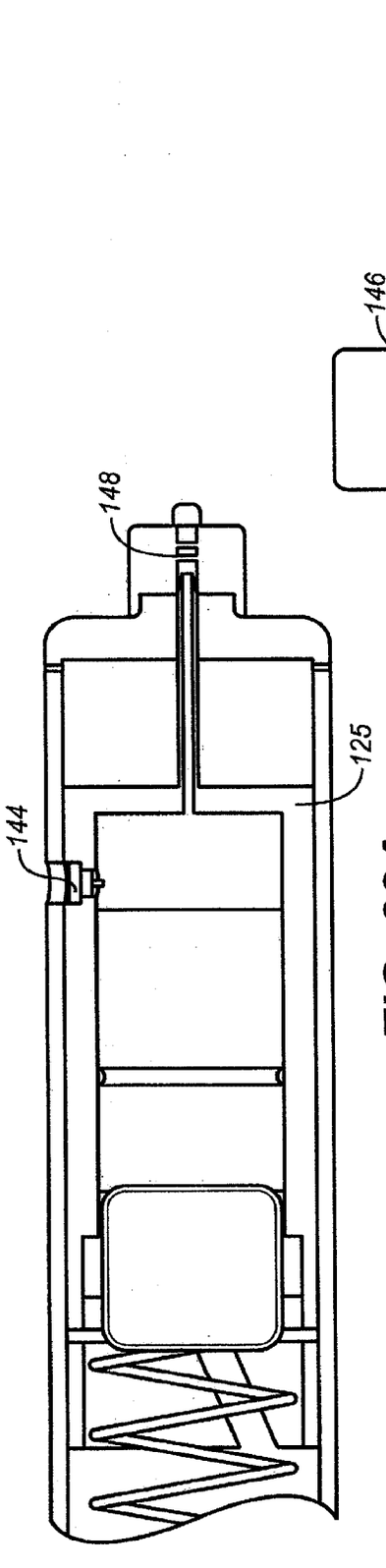



FIG. 33A

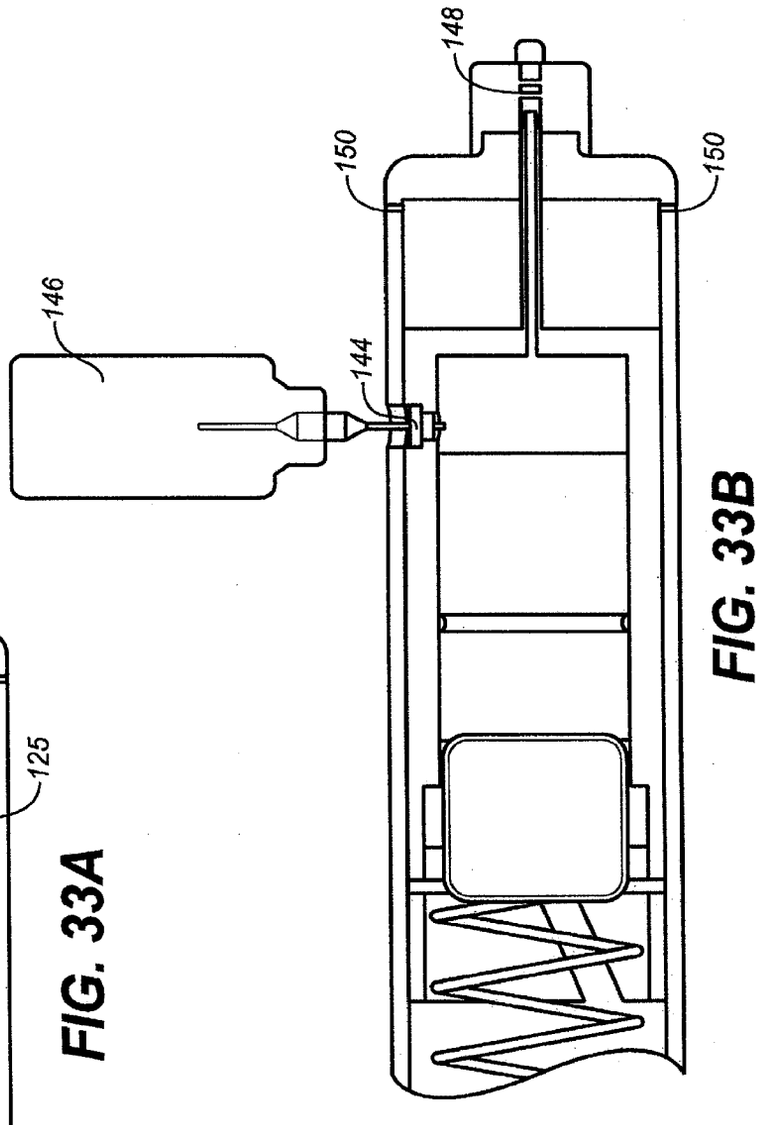



FIG. 33B

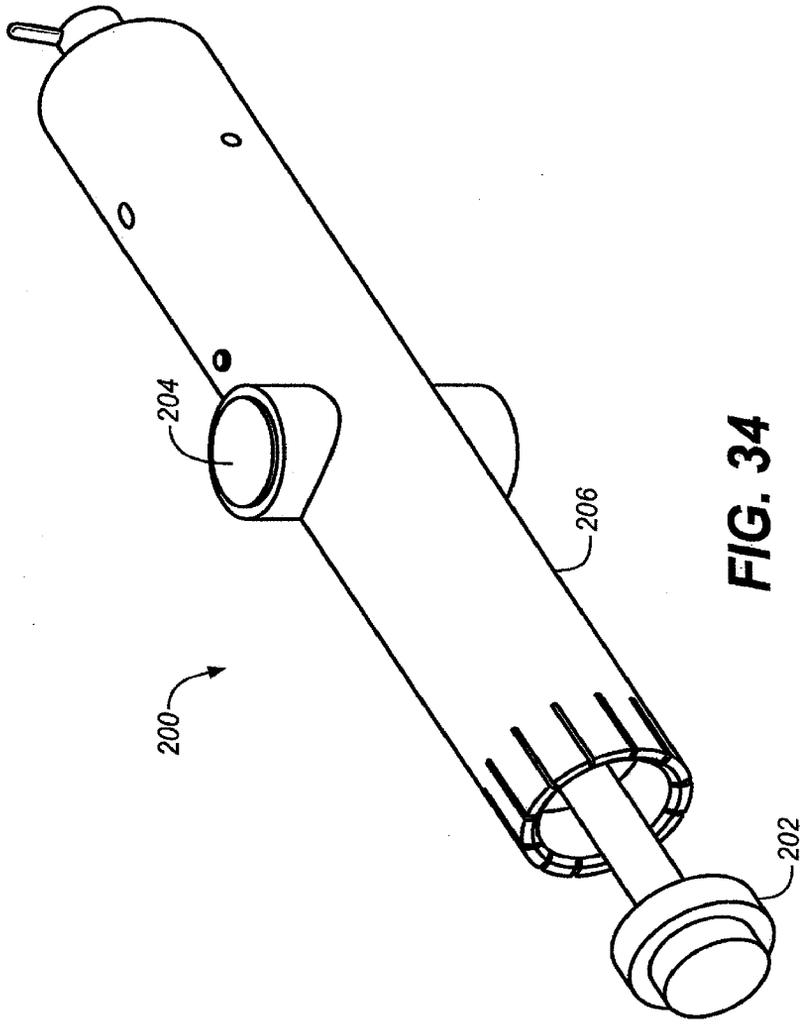



FIG. 34

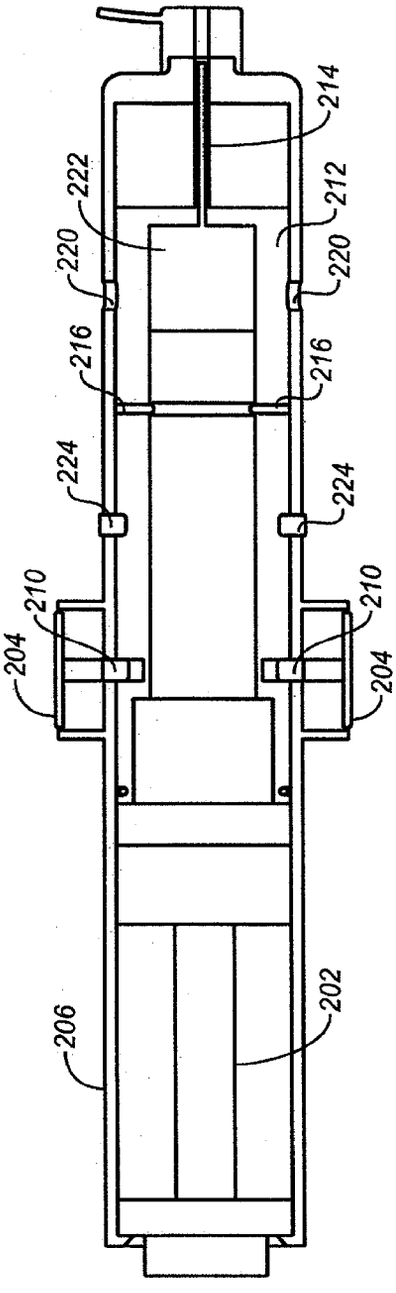



FIG. 35A

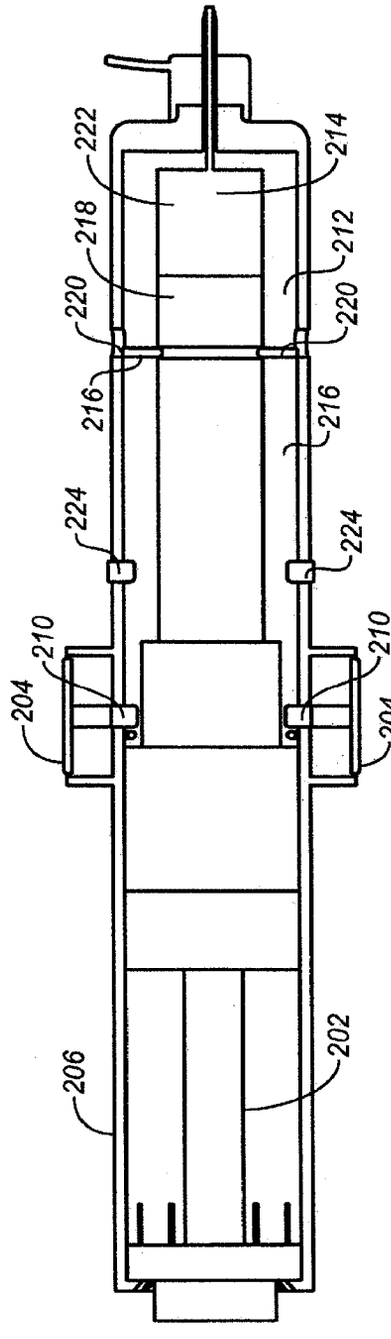



FIG. 35B

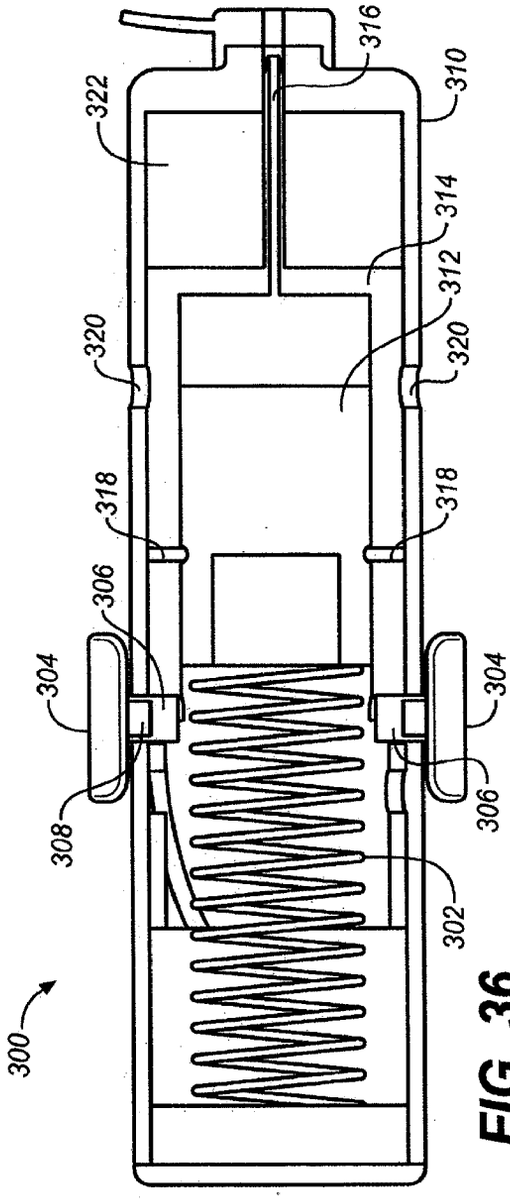



FIG. 36

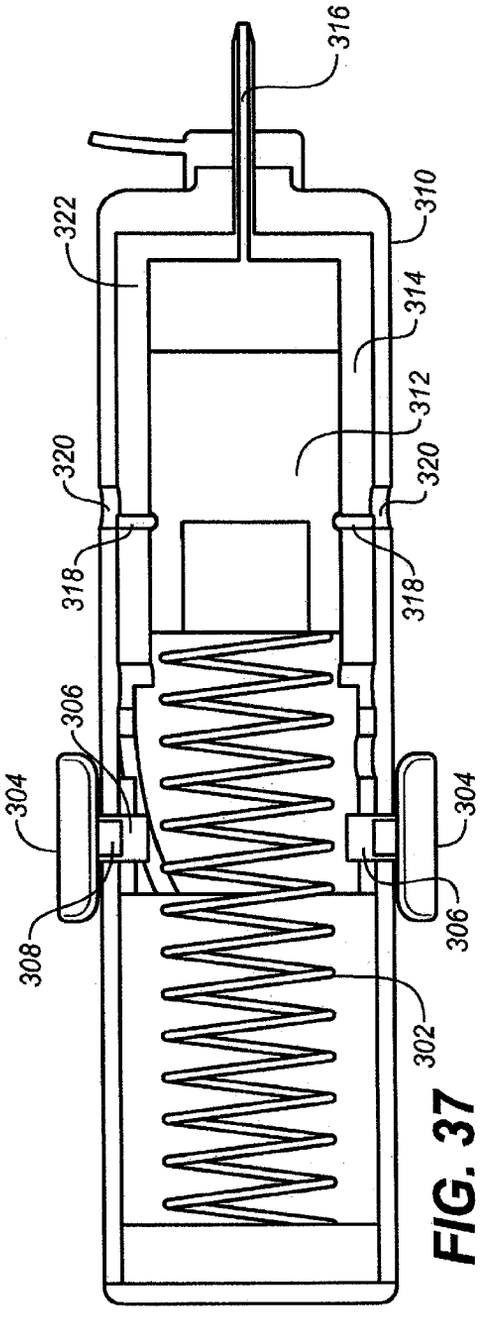



FIG. 37

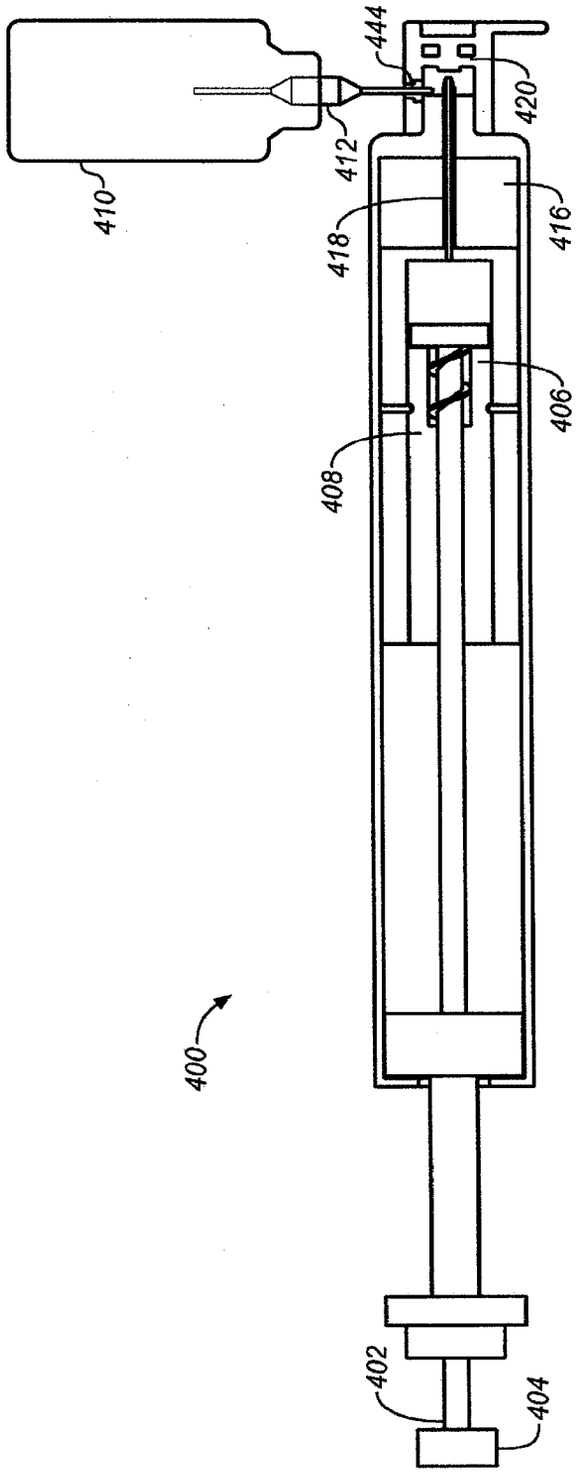



FIG. 38

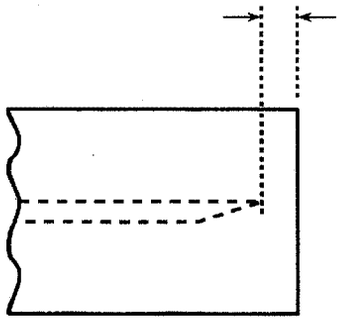


FIG. 39A

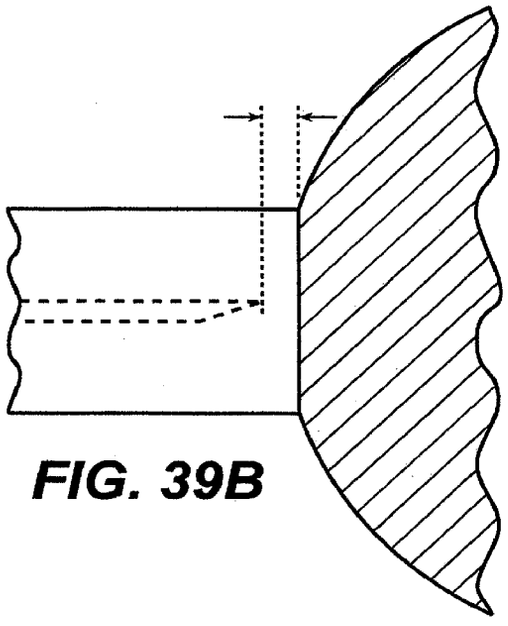


FIG. 39B

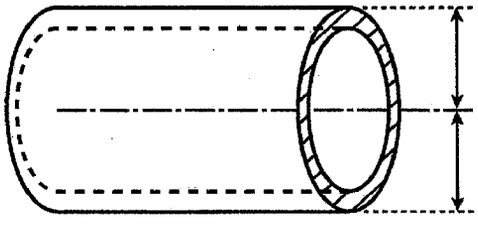


FIG. 39C

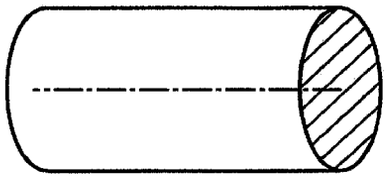


FIG. 39D

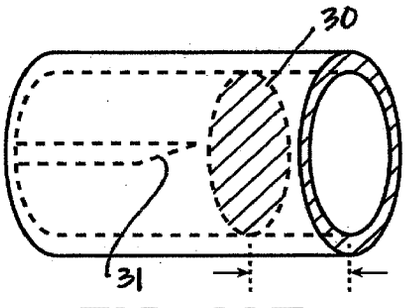



FIG. 39E

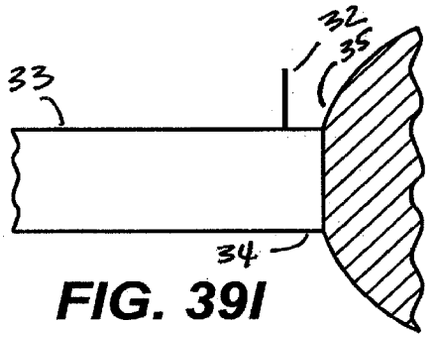



FIG. 39I

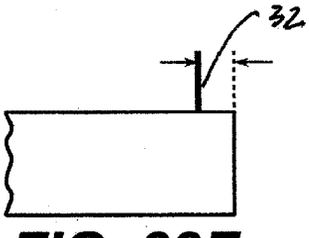



FIG. 39F

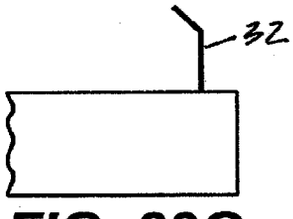



FIG. 39G

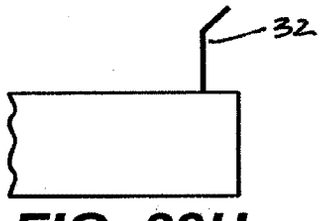



FIG. 39H

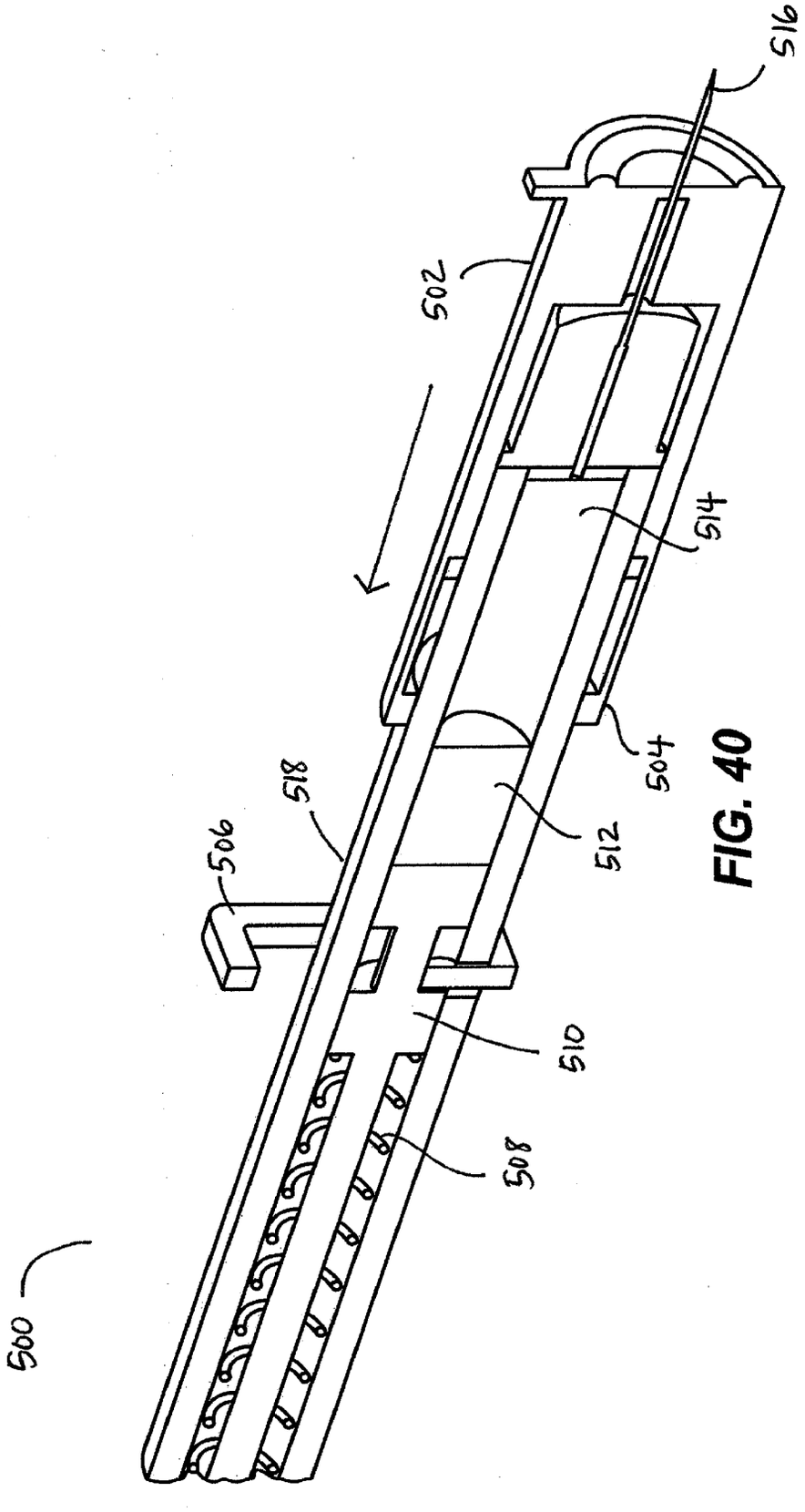



FIG. 40

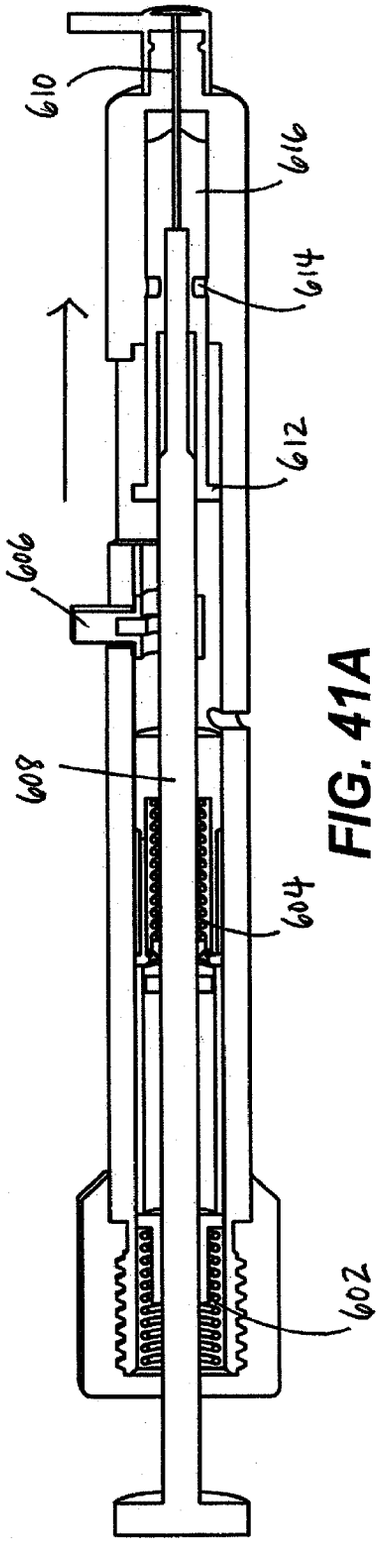



FIG. 41A

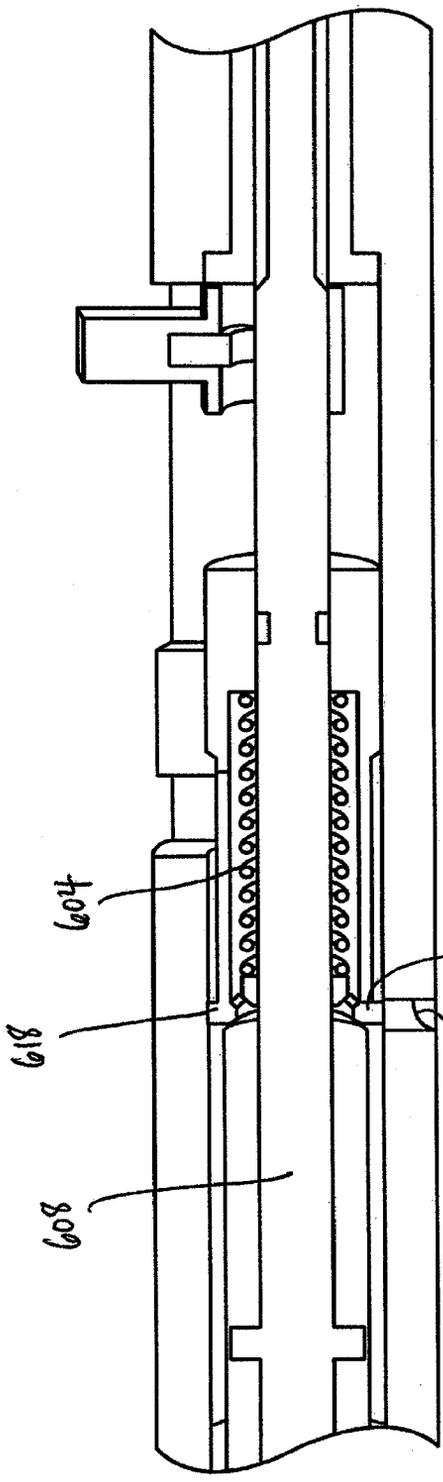



FIG. 41B

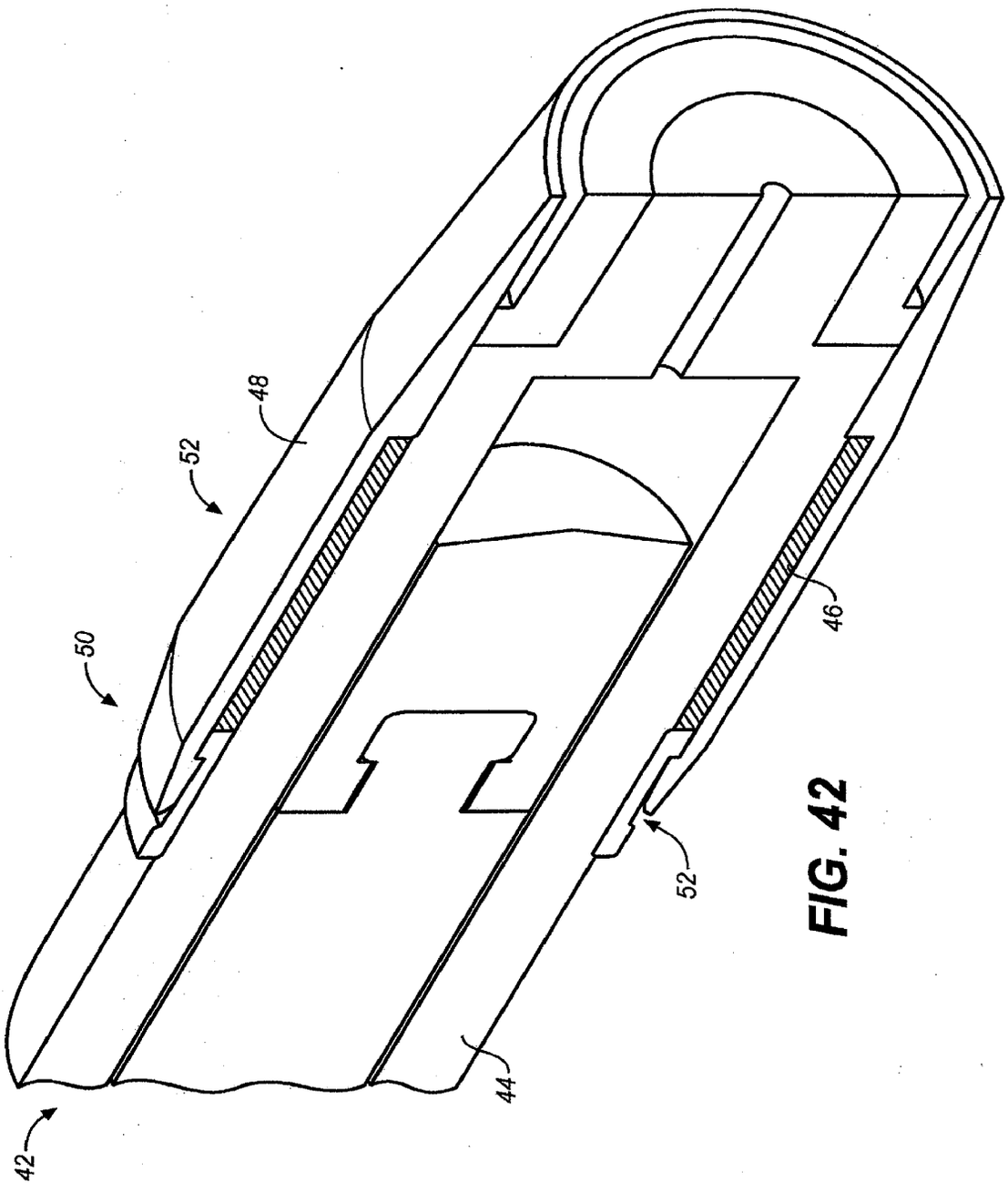



FIG. 42

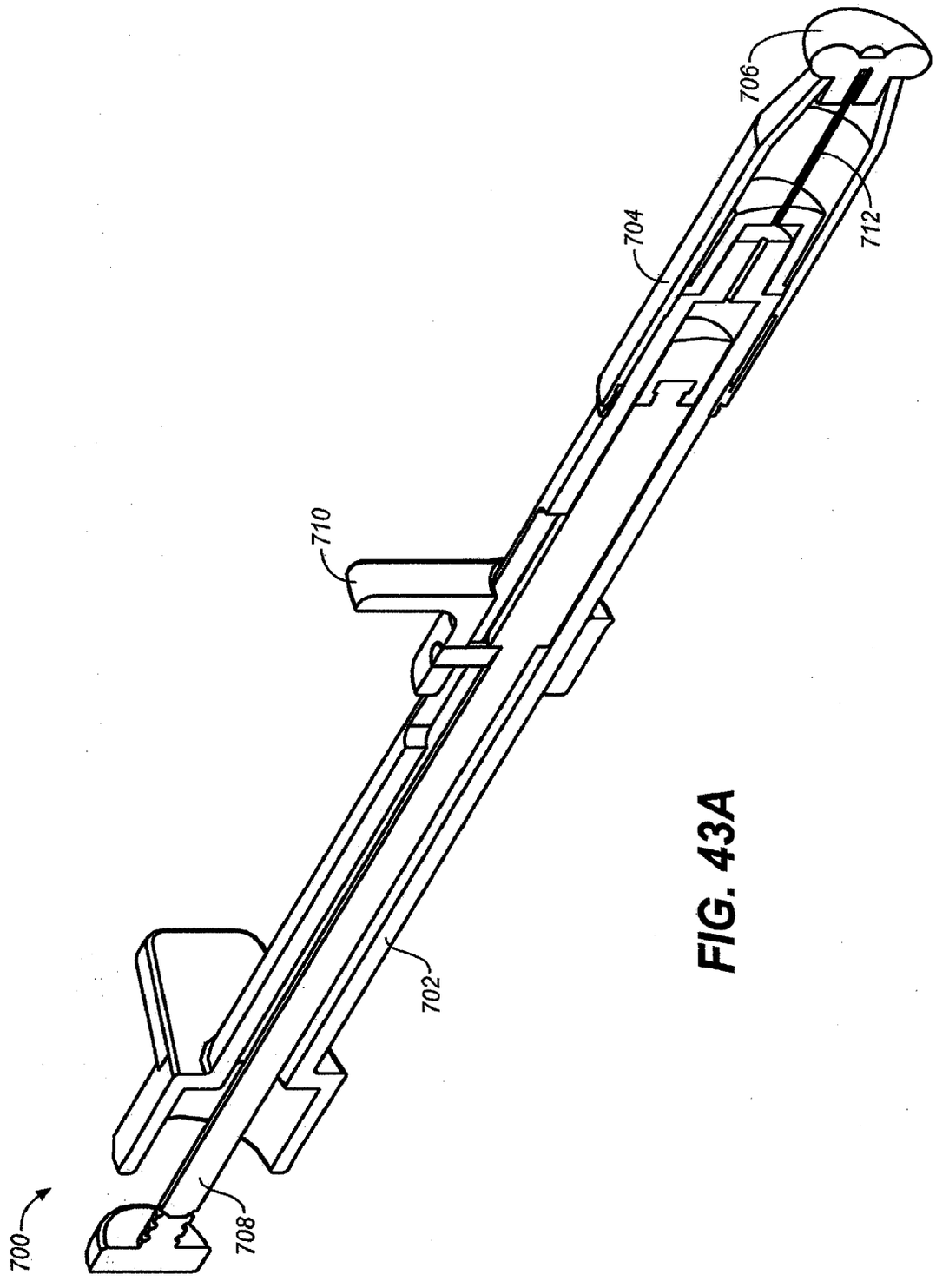



FIG. 43A

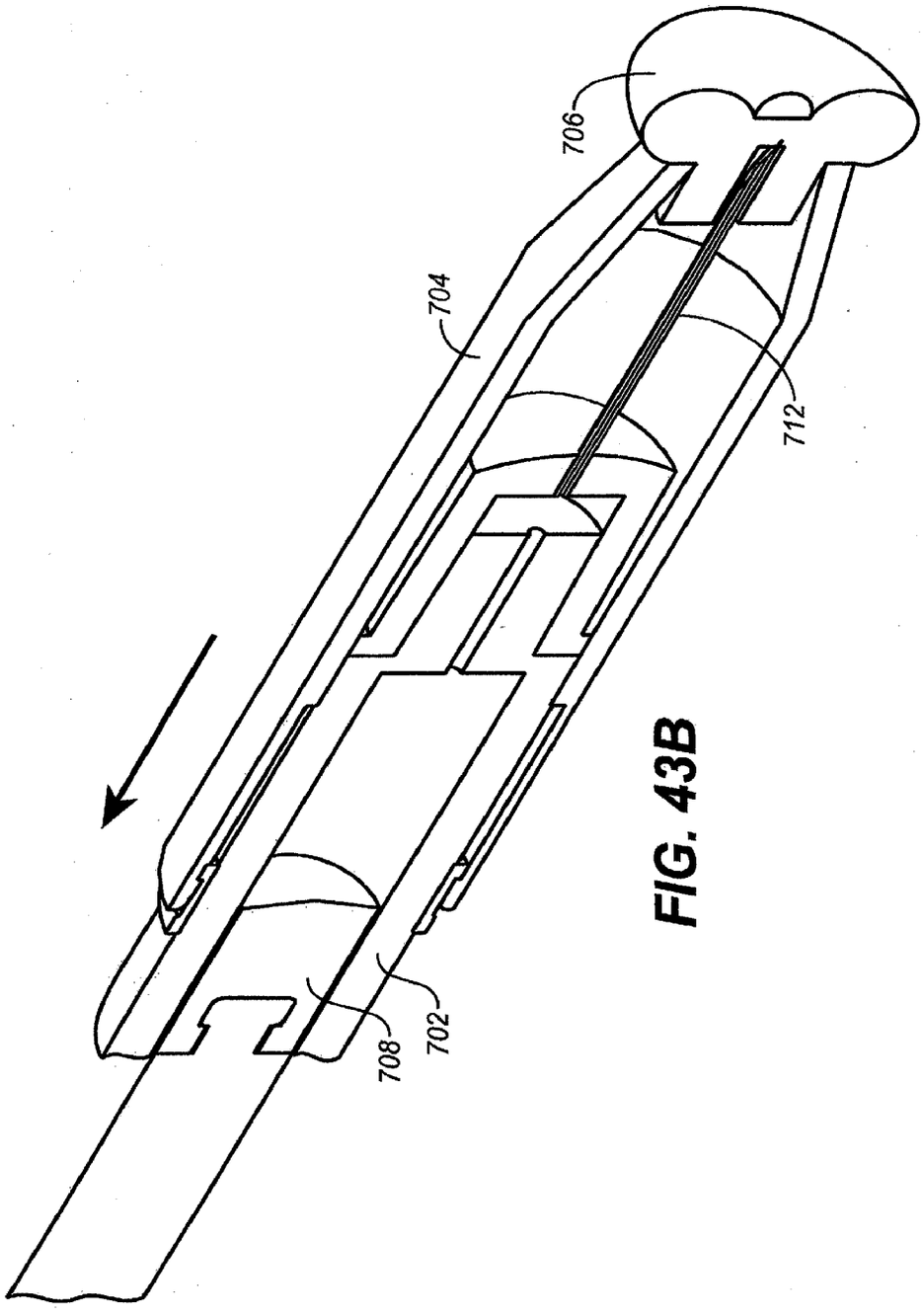



FIG. 43B

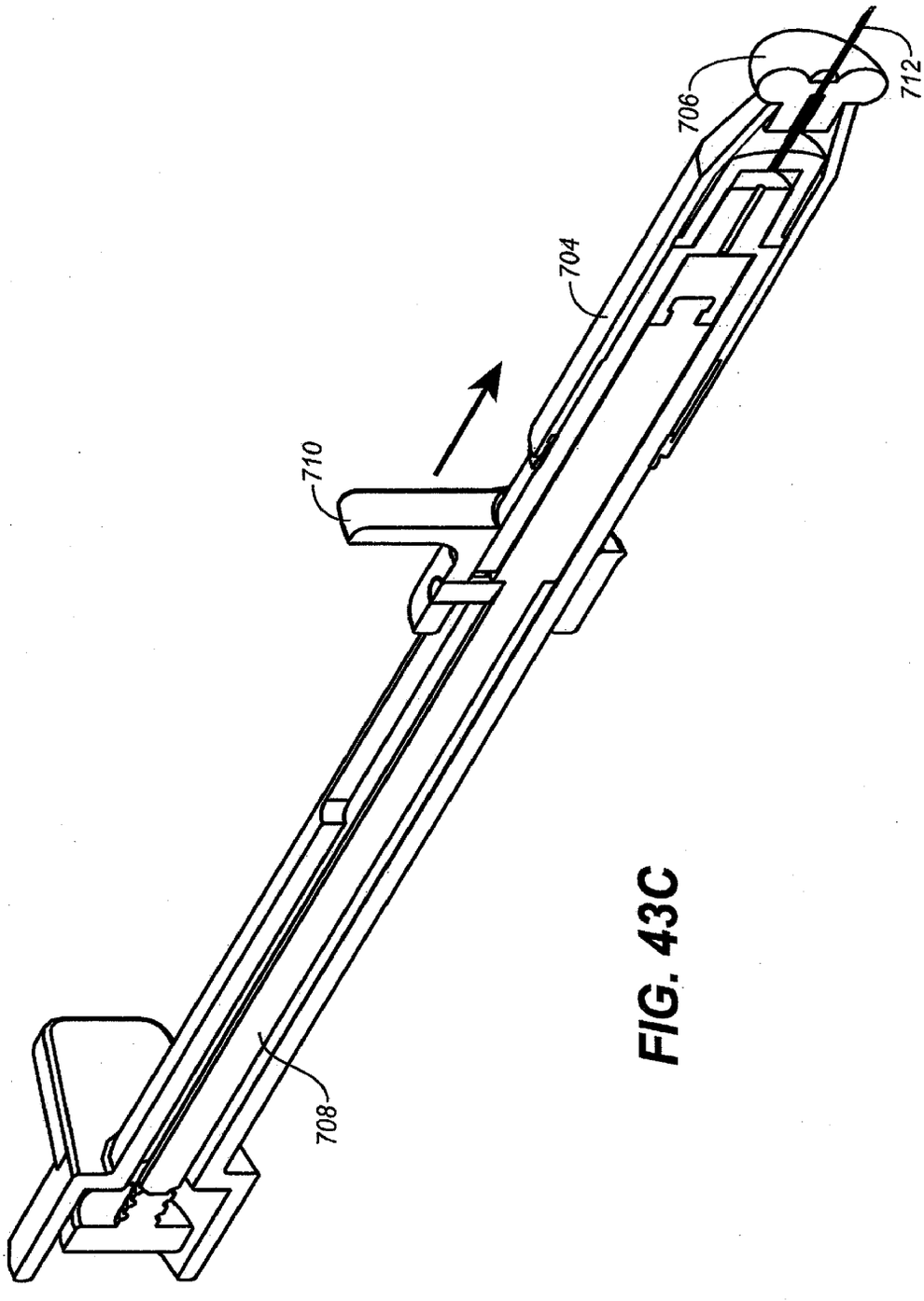



FIG. 43C

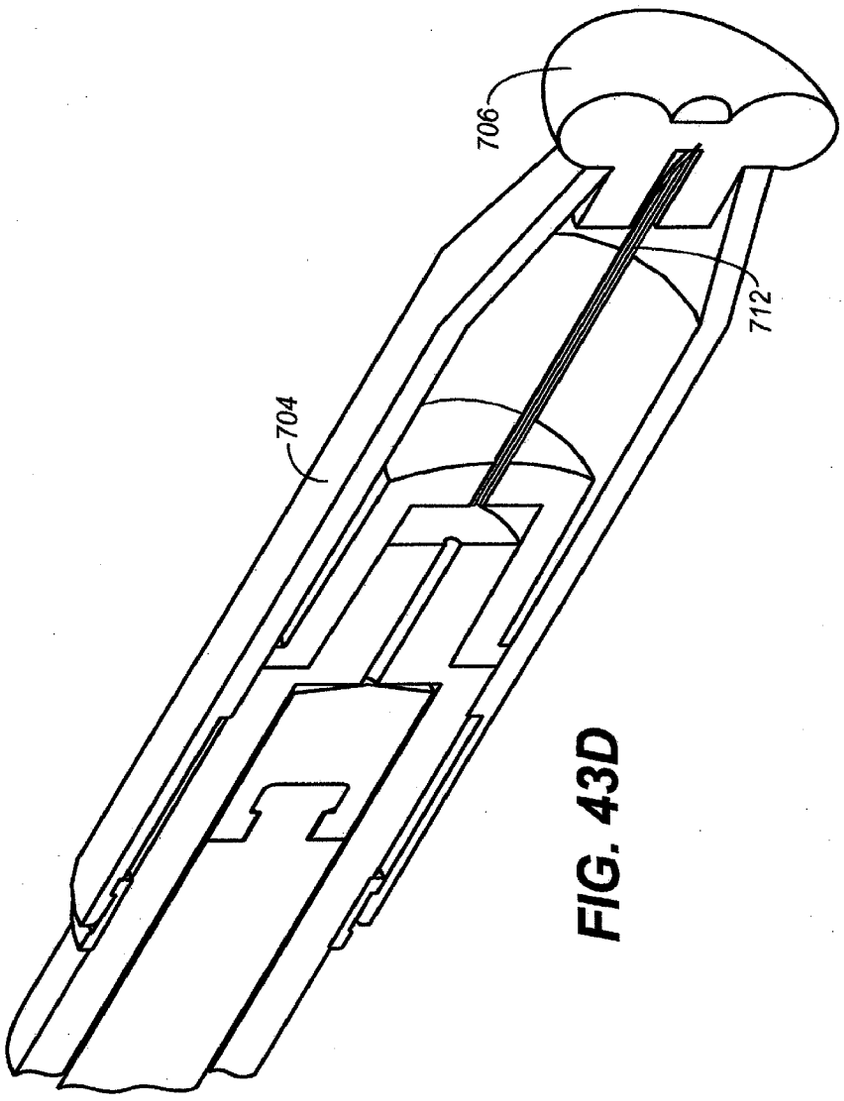



FIG. 43D

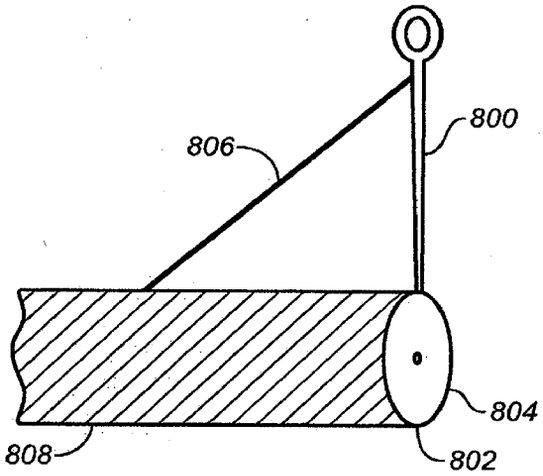



FIG. 44A

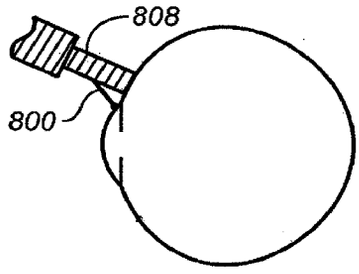



FIG. 44B

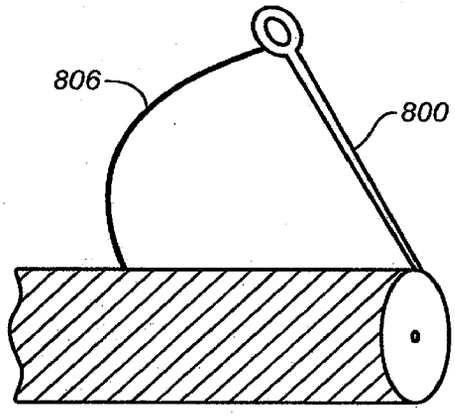



FIG. 44C

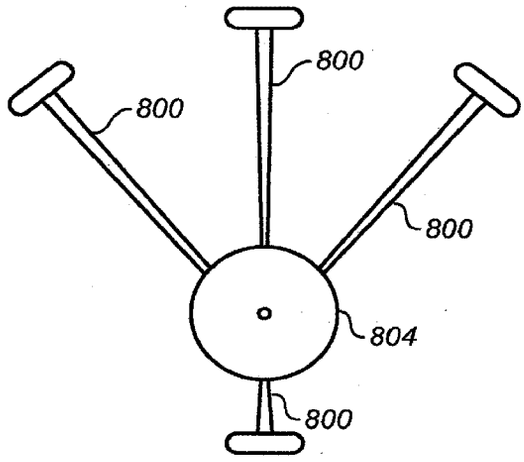



FIG. 44D

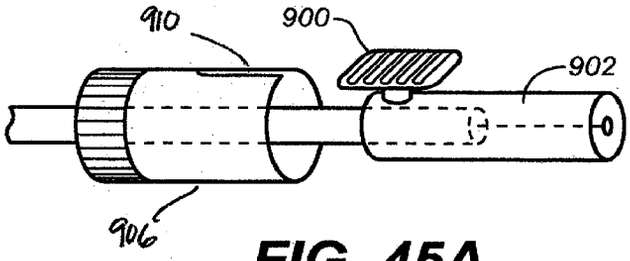



FIG. 45A

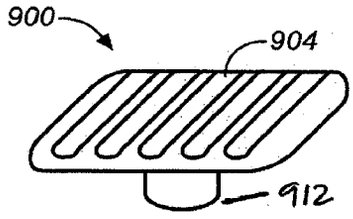



FIG. 45B

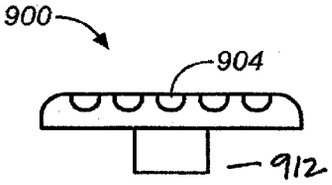



FIG. 45C

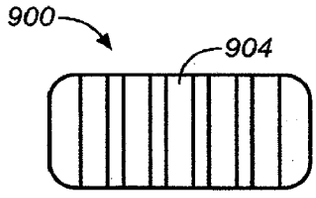



FIG. 45D

FIG. 45E

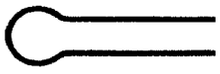


FIG. 45F

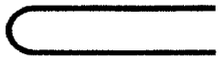


FIG. 45G

FIG. 45H

FIG. 45I

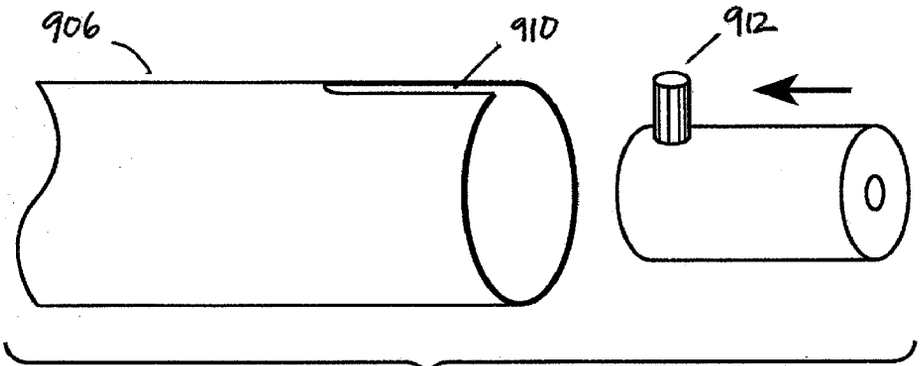



FIG. 45J

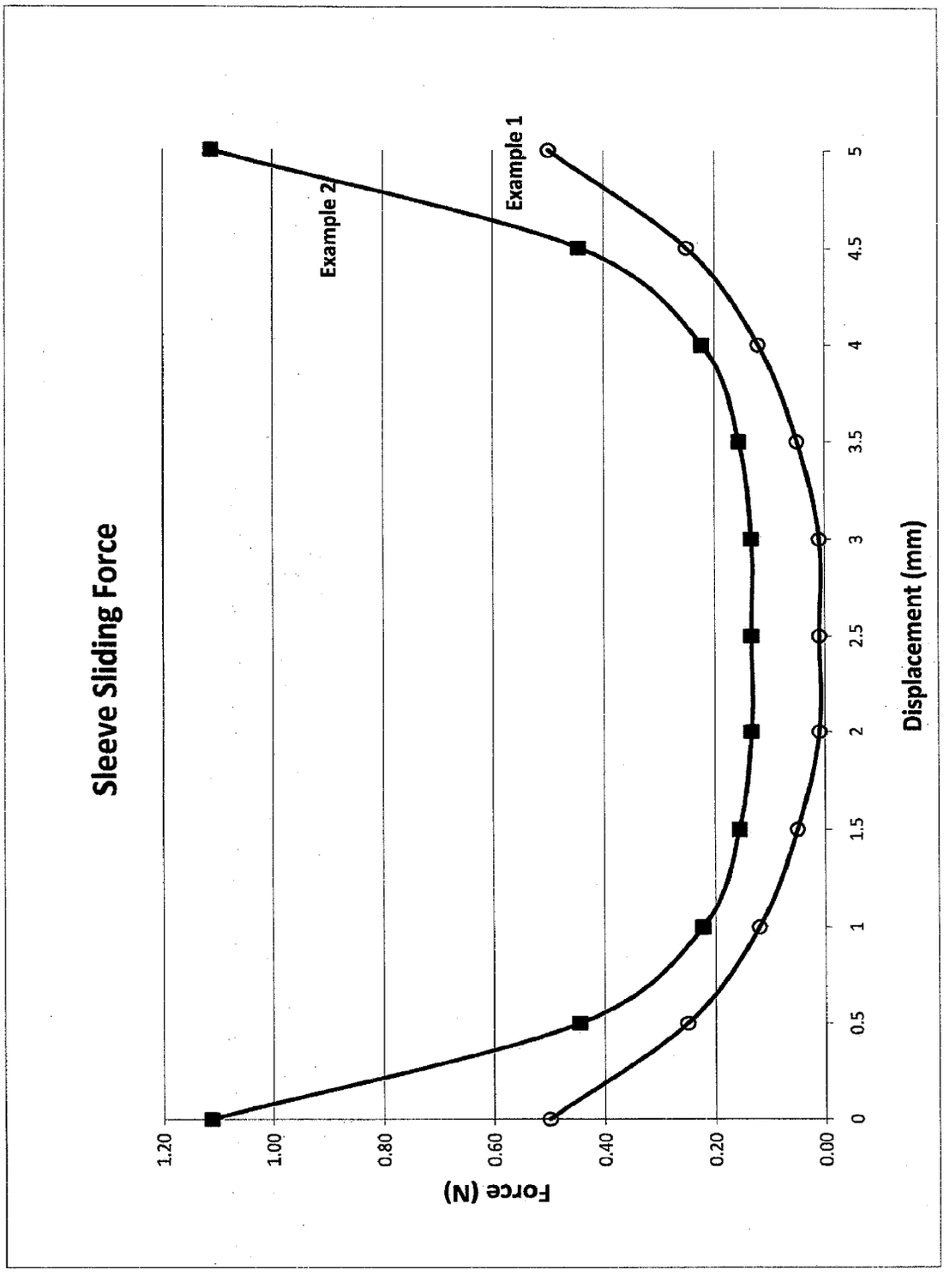



FIG. 46

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 11/30840

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61F 2/00 (2011.01)
USPC - 424/427-428
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC - 424/427-428

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 604/93.01, 294, 521 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWest: PGPB,USPT,USOC,EPAB,JPAB; Google; ocular, eye, eyeball, contact, surface sclera, limbus, guide, measure, spring, plunger, actuator, needle, conduit, lumen, inject

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | US 2010/0030150 A1 (PAQUES et al.) 04 February 2010 (04.02.2010) Figs 1, 3 and 25; para [0050]-[0051], [0056], [0058]-[0059], [0061], [0063]-[0064], [0066], [0076], [0092], [0094], [0097], [0101], [0110], [0116], [0118]-[0121], [0127], [0131] | 1-13, 15-17, 20-23, 26-27, 29-32, 35-36, 38, 40-60, 64-94 |
| --- | | --- |
| Y | | 14, 18-19, 24-25, 28, 33-34, 37, 39, 61-63 |
| Y | US 7,678,078 B1 (PEYMAN et al.) 16 March 2010 (16.03.2010) col 4, ln 53-55; col 12, ln 60-64; col 14, ln 48-51; col 15, ln 8-9 | 14, 18-19, 39 |
| Y | US 2001/0008961 A1 (HECKER et al.) 19 July 2001 (19.07.2001) para [0093], [0127] | 24-25, 28, 33-34, 37, 61-63 |
| A | US 2003/0060763 A1 (PENFOLD et al.) 27 March 2003 (27.03.2003) entire document | 1-94 |
| A | US 2007/0005016 A1 (WILLIAMS) 04 January 2007 (04.01.2007) entire document | 1-94 |

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

* Special categories of cited documents:
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"O" document referring to an oral disclosure, use, exhibition or other means
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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
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| 18 May 2011 (18.05.2011) | 27 MAY 2011 |
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*[Continued on next page]*

(54) Title: DOSE GUIDES FOR INJECTION SYRINGE

(57) Abstract: The present embodiments provide for simple devices that guide the loading and dispensing of accurate small doses of fluid from standard injection syringes.

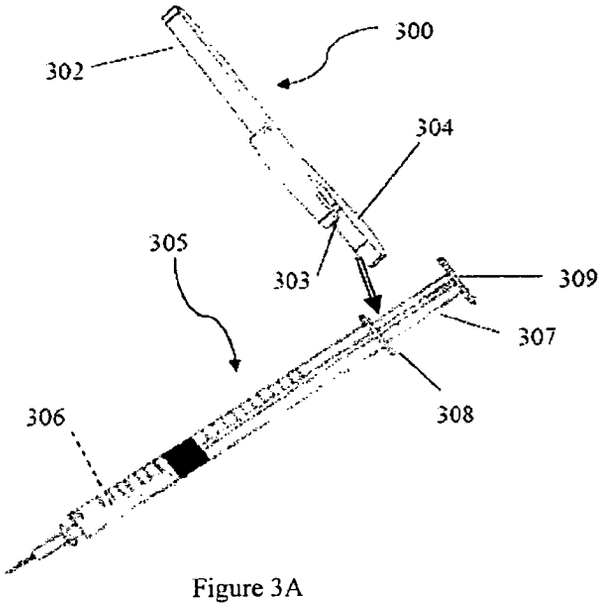


Figure 3A

WO 2012/149040 A2

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# DOSE GUIDES FOR INJECTION SYRINGE

## RELATED APPLICATIONS

**[0001]** The present application claimed priority benefit of U.S. Patent Appls. Ser. No. 61/478,748, filed April 25, 2011, and Ser. No. 61/597,248, filed February 10, 2012, each of which is incorporated fully herein by reference.

## BACKGROUND

**[0002]** A hypodermic syringe is an important piece of medical equipment for many individuals ranging from surgeons to patients. With advancements in modern medicine, shorter needles, longer reservoirs, and virtually painless injections, syringes have changed for the better. Nevertheless, it remains difficult for even skilled practitioners to load a syringe with precise volumes and administer the unit volume (e.g., dose) accurately. This is particularly important for injections where variations can result in adverse clinical effects, such as highly potent medicines (e.g., insulin), in certain settings where small doses are administered (e.g., intraocular injections), or where the care giver is less skilled or has difficulty handling the syringe loading process. There is a need in the art for simple yet accurate means for loading and delivering more accurate volumes using standard syringes.

## SUMMARY

**[0003]** The present invention provides for a system comprising at least one device that allows for accurate loading and/or delivery of precise volumes of fluid (e.g., sample or medicament) using a standard injection syringe.

**[0004]** In some aspects of the invention, the system comprises a removable dose-loading "spacer" guide of predetermined dimensions that, in use, is placed abutting the end of a standard syringe where the plunger extends from the syringe barrel (typically placed slidably adjacent to the plunger) that is loaded with an excess of fluid (e.g., medicine), from which the excess fluid is then expelled as regulated by the spacer guide to provide for an accurate loading of fluid volume (e.g., unit dose) within the syringe. The dose-loading spacer is then removed from the syringe/plunger junction, and the remaining volume (dose) can be delivered from the syringe.

**[0005]** In other aspects, the system comprises a dose-delivery guide of predetermined dimensions, used to deliver an accurate dose to the subject. In use, the dose-delivery guide is placed abutting the top of the barrel of a syringe (i.e., where the plunger extends from the barrel) either before or after the syringe has been loaded with fluid, then the fluid (e.g., dose of medicine) is delivered to the subject by depression of the plunger, wherein the dose-delivery

guide regulates the delivery of the dose volume by stopping the motion of the plunger according to the predetermined parameters of the dose-delivery guide. In a particular aspect, the dose-delivery guide is integral to the proximal end of the plunger rod.

[0006] In another aspect, the dose-loading spacer and the dose-delivery guide are used synergistically to provide for an accurate delivery of the dose. The dose-loading spacer defines the volume of the fluid prior to administration and the dose-delivery guide assures a more accurate delivery of the dose. The dose-delivery guide may be positioned before or after the syringe has been filled with fluid (e.g., medicine); or before or after the dose-loading spacer has been used. If the dose-delivery guide is in place at the top of the syringes barrel, the dose-loading spacer is positioned either over the dose-delivery guide (i.e., encompassing the guide) or adjacent to the dose-delivery guide (e.g., abutting the guide and the plunger), depending on the predetermined parameters of the dose-loading spacer, typically but not necessarily after the syringe has been filled with an excess of fluid. The excess fluid expelled according to the spacer to provide an accurate dose loaded in the syringe; then the dose loading spacer is removed but the dose-delivery guide is left in place, such that the remaining fluid (dose) is delivered to the subject by depression of the plunger, wherein the dose-delivery guide regulates the delivery of the dose volume by stopping the motion of the plunger according to the predetermined parameters of the dose-delivery guide. In a specific embodiment, the dose-delivery guide is integral to the plunger for use with a standard glass syringe such as BD 0.5 cc Hypak™ glass syringe.

[0007] Using the system of the dose-loading spacer and, optionally, the dose-delivery guide is relatively easy, such that elderly patients or children of appropriate age (e.g., diabetics who inject insulin at home), can achieve precise dosing easily and accurately.

[0008] A particular aspect of the invention is a dose-loading "spacer" guide for loading an injection syringe, the spacer having a grip portion and a collar portion, the collar portion configured to be placed at the proximal (top) end of a syringe barrel, slidably abutting an extended syringe plunger rod; wherein the collar is rigid and includes an opening for receiving the extended syringe plunger, and an inner wall that bears against the plunger rod for guided displacement therealong, and wherein the collar has predetermined dimensions and, in use, stops the movement of the plunger toward the syringe barrel at a predetermined distance from the syringe barrel, which distance is directly related to the volume to be loaded in the injection syringe.

[0009] Another particular aspect of the invention is a dose-delivery guide for controlling the volume expelled from a loaded injection syringe, the dose-delivery guide configured to be at the proximal (top) end of a syringe barrel, slidably abutting an extended syringe plunger rod;

wherein the dose-delivery guide is rigid in length and includes an opening for receiving the extended syringe plunger rod, which opening allows the plunger to move freely through the guide until motion of the plunger is impeded by the guide, wherein the dose-delivery guide has predetermined dimensions and a rigid height that, in use, stops the movement of the plunger toward the syringe barrel at a predetermined distance from the syringe barrel, which distance is related to the volume (dose) to be delivered by the injection syringe. The dose-delivery guide can have a continuous circumference for placement onto a syringe plunger before the plunger is engaged with the syringe, or can have a discontinuous circumference for placement onto a plunger that is already engaged with the syringe. The dose-delivery guide may be integral to the plunger rod. In a specific embodiment, the dose-delivery guide is integral to the plunger for use with a standard glass syringe such as BD 0.5 cc Hypak™ glass syringe.

**[00010]** Another aspect of the invention is a dose-loading dose-delivery system comprising both a dose-loading "spacer" guide and a dose-delivery guide for loading and expelling the volume (dose) of a syringe. In use, for example, the dose-delivery guide is placed at the top (proximal end) of the syringe barrel, typically steadied against the plunger rod, either before or after the plunger is engaged with the syringe; excess fluid is loaded into the syringe or the syringe may have been preloaded with excess fluid; the dose-loading spacer is placed over, or adjacent to, the dose-delivery guide, and excess fluid is expelled from the syringe as determined by the dose-loading spacer (i.e., the plunger is depressed until its motion is stopped by the dose-loading spacer) and the dose-loading spacer is removed; remaining fluid in the syringe is then delivered to the subject by depressing the plunger until the plunger's motion is stopped by the dose-delivery guide.

**[00011]** Alternatively, the invention is a dose-loading dose-delivery system comprises a removeable dose-loading "spacer" guide and a dose-delivery guide integral to the plunger rod for loading and expelling the volume (dose) of a syringe. In use, for example, the syringe has been preloaded or is loaded with excess fluid; the dose-loading spacer is placed over, or adjacent to, the dose-delivery guide; excess fluid is expelled from the syringe as determined by the dose-loading spacer (i.e., the plunger is depressed until its motion is stopped by the dose-loading spacer); the dose-loading spacer is removed; remaining fluid in the syringe is then delivered to the subject by depressing the plunger until the plunger's motion is stopped by the dose-delivery guide.

## DESCRIPTION OF THE DRAWINGS

**[00012]** Figure 1A is a photograph showing the top view of an embodiment of the invention. Figure 1B shows a side view of an embodiment of the invention.

**[00013]** Figures 2A and 2B are schematic diagrams showing dimensions of an embodiment of the invention. "N.T.S." indicates drawings are not to scale.

**[00014]** Figures 3A to 3D illustrate use of an embodiment of the dose-loading spacer with a conventional syringe. In Figure 3A, the syringe has been loaded with an excess volume of fluid; double arrow indicates the movement of the spacer into position. In Figure 3B, the syringe guide has been placed at the proximal (top) end of the syringe barrel, abutting the plunger rod; double arrow indicates motion of the plunger. In Figure 3C, the plunger has been depressed against the dose-loading spacer, which has regulated the expulsion of the excess fluid but caused the syringe to retain an accurate and pre-determined amount of fluid. In Figure 3D, the guide has been removed, and the syringe contains the accurate dose as determined by the guide. The devices in the drawings of Figure 3 are not to scale.

**[00015]** Figure 4A is a photograph of a syringe bearing an example dose-delivery guide that has been placed on the syringe plunger rod (arrow), and an example removable dose-loading spacer. Figure 4B is a photograph of the syringe of Figure 4A with the dose-loading spacer placed adjacent to the dose-delivery guide, illustrating how the guides can be configured to fit together.

**[00016]** Figure 5A and 5B are photographs of example dose-loading and dose-delivery guides with predetermined measurements correlated with the volume to be loaded and delivered. In this embodiment, the dose-delivery guide has a greater length dimension than the dose-loading guide because the syringe flange at the proximal end of the barrel has an indentation that receives the dose-delivery guide to the depth of 0.6mm. * indicates critical measurement: tolerance should be within ± 0.02 mm. ID: inner dimension; OD: outer dimension.

## DETAILED DESCRIPTION

**[00017]** It should be understood that this invention is not limited to the particular methodology, protocols, and reagents, etc., described herein and as such may vary. The terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention, which is defined solely by the claims.

**[00018]** As used herein and in the claims, the singular forms include the plural reference and vice versa unless the context clearly indicates otherwise. The term "or" is inclusive unless modified, for example, by "either." Other than in the operating examples, or where otherwise indicated, all numbers expressing quantities of ingredients or reaction conditions used herein should be understood as modified in all instances by the term "about."

**[00019]** All patents and other publications identified are expressly incorporated herein by reference for the purpose of describing and disclosing, for example, the methodologies described

in such publications that might be used in connection with the present invention. These publications are provided solely for their disclosure prior to the filing date of the present application. Nothing in this regard should be construed as an admission that the inventors are not entitled to antedate such disclosure by virtue of prior invention or for any other reason. All statements as to the date or representation as to the contents of these documents is based on the information available to the applicants and does not constitute any admission as to the correctness of the dates or contents of these documents.

**[00020]** Unless defined otherwise, all technical and scientific terms used herein have the same meaning as those commonly understood to one of ordinary skill in the art to which this invention pertains. Although any known methods, devices, and materials may be used in the practice or testing of the invention, the methods, devices, and materials in this regard are described herein.

**[00021]** An embodiment of the present invention provides for a dose-loading "spacer" guide for loading the correct volume of fluid (e.g., unit dose) in a standard hypodermic syringe. The term dose-loading spacer is synonymous with dose-loading guide, but in some instances herein, "spacer" is used to further distinguish from the dose-delivery guide described herein. The dose-loading spacer may be made of any suitably rigid material, such as plastic or metal (including recycled materials) that can be sterilized or otherwise cleaned for use. It may be removable or permanent in nature. The dose-loading guide may be reusable and long-lasting, or it may be disposable for single-use.

**[00022]** The dimensions of the spacer, particularly the height of the interior wall of the collar portion, for example as shown as (104) of Figure 1, are designed in relation to the volume of the syringe to be used in conjunction with the guide. This relationship can be expressed as:

$$v = \pi r^2 h$$

where "v" is the unit volume μL (or cubic mm) to be delivered by the syringe; "r" is the mm radius of the interior of the syringe cylinder; and "h" is the mm length that the plunger has to travel to deliver the unit volume. For example, in a Becton Dickenson 28 gauge insulin syringe (product no. 309300), r = 1.475 mm (one-half of the diameter of 2.95 mm). In this syringe, every 1 mm in length corresponds to 6.83 μL volume. If the unit volume to be delivered is 7.5 μL, (i.e., v = 7.5); a spacer having a collar height of 1.1 mm (i.e. h = 1.1 mm) can be used to measure a 7.5 μL dose (i.e., $7.514 = (3.14)(1.475)^2(1.1)$. Thus, one skilled in the art can use the volume dose and diameter of a given syringe to design the corresponding collar dimension. In a particular embodiment, a guide having a 1.1 mm collar is used to accurately load a 7.5 μL dose.

**[00023]** The handle portion of the spacer may be of any practical design (e.g., shape or texture) that allows the user to grip the guide for placement on (and, optionally, removal from)

the syringe, e.g., on the top of the syringe barrel abutting the plunger rod. The handle portion may be manufactured contiguous to the collar, or may be connected (either detachably or fixed) to the collar portion by any other approach. The dose-loading guide may also bear a label or instruction(s).

**[00024]** As noted, the dose-loading guide of the present invention may be used with commercially available syringes. Because the spacer is useful for accurately loading small volumes, typically the syringe used will be for small-dose administration, such as a tuberculin syringe (Becton Dickinson, Franklin Lakes, NJ) or an insulin syringe (Becton Dickinson), for example, BD 3/10 cc Insulin Syringe, or BD 0.5 cc Hypak™ glass syringe. The present dose-loading guide can also be used in other applications where accurate and repeatable volumes are required, for example syringes used to load chromatography samples such as HPLC or autosampler syringes (e.g., Hamilton Syringes, Sigma Aldrich, St. Louis, MO).

**[00025]** In use, the hypodermic syringe is loaded with fluid (e.g., medicine, drug, formulation, therapeutic agent, placebo, or sample) in excess of the amount needed for the actual dose. Air bubbles may be tapped out of the syringe and needle. The dose-loading guide is then placed on the proximal (top) end of the syringe barrel, abutting the plunger rod (typically where the plunger enters the syringe barrel), and the plunger depressed until the collar portion of the spacer stops the motion of the plunger. In this process, excess fluid is expelled from the syringe, leaving an accurate dose loaded in the barrel of the syringe as determined by the size of the collar portion of the dose-loading spacer. The guide may then removed, such that the plunger may be depressed fully as the dose is delivered. For example, a dose-loading guide can be used to accurately load 7.5 μL using a standard, commercially available tuberculin syringe.

**[00026]** Referring to the Drawings, Figure 1 shows an embodiment of the syringe dose-loading guide/spacer (100). The spacer has a grip portion (101) that serves as a handle or other means whereby the user can position the guide. The guide has a collar portion (102) that defines an opening (103) that is, in use, placed by the user such that it abuts the top end of a standard syringe. In use, the movement of the plunger rod into the barrel of the syringe is impeded by the height of the spacer (104). Figure 2 presents measurements of particular parts of a dose-loading spacer embodiment.

**[00027]** Referring to Figure 3, a standard, commercially available syringe (305) is loaded with formulation for injection (306), in an amount in excess of the desired dose. The guide (300) may be held by the grip portion (301) such that the collar portion (302) opening (303) abuts the proximal end of the syringe barrel (308), e.g., at the distal end of the extended syringe plunger rod (307). As indicated by the double arrow in Figure 3B, the plunger (307) is then depressed into the barrel of the syringe (305) until the proximal end of the plunger (309) contacts the guide

(300), as shown in Figure 3C. Thus, the dose remaining in the syringe (306) is regulated directly by the dimension of the guide (304). Then, the guide may be removed, as shown in Figure 3D, and the syringe is ready for the delivery (e.g., administration) of the accurately loaded dose.

**[00028]** Another aspect of the invention provides for a dose-delivery guide that can used without or in conjunction with a dose-loading guide to accurately deliver small volumes of fluid (e.g., medicament, pharmaceutical composition, sample, etc.) to a target (e.g., a subject or device). The dose-delivery guide has predetermined dimensions, designed to fit at the top (proximal) end of a standard syringe or integral to the plunger rod. The guide is optimally designed to remain stably in place on the syringe during use and does not have to be held in place by the user as the syringe is being used to deliver the dose. For example, the guide may be shaped to fit along and substantially around a syringe plunger rod and allow the plunger rod to move through the guide, or the guide may be integral to the plunger rod. This configuration allows the user to inject the syringe with one hand holding the syringe and the other hand free for any particular use. The circumference of the dose-delivery guide may be deformable or rigid, continuous or non-continuous, such that it may be placed abutting the syringe plunger either before or after the plunger is engaged with its syringe, respectively. The guide may be removable or permanent. The guide may be configured to be placed on the syringe either before or after the syringe is loaded. The dose-delivery guide must maintain rigidity along its height (i.e., the dimension related to the dose volume). The dose-delivery guide may be made of any suitable material, e.g., metal or sterilizable plastic, which maintains dimension along the length of the guide.

**[00029]** The use of the dual dose-loading and dose-delivery system is advantageous where syringe devices have deformable plunger/syringe interfaces, such as rubber ends, where the pressure exerted by the user can lead to a larger volume being delivered than is intended. Because the distance the plunger travels within the syringe barrel is fixed by the height of the dose-loading spacer and the height of the dose-delivery guide (rather than the depression of the plunger against the syringe), a more precise and accurate volume of medication can be administered. The difference in the dimensions of the height of the dose-loading spacer and the height of the dose-delivery guide are calculated from the formula:

$$V = \pi r^2 h$$

where V is the volume delivered, r is the radius of the inner dimension of the syringe barrel and h is the distance the piston has to travel along the length of the syringe barrel. For example, if the dose volume to be delivered is 7.5 μL, then:

$V = 7.5\ \mu L$ or $7.5\ mm^3$

$r = 2.3$ mm (diameter was measured to be 4.6 mm)

$V = \pi r^2 h$, or $h = V / \pi r^2$

$h = 7.5\ mm^3 / (3.14)\ (2.3\ mm)\ (2.3\ mm) = 0.45\ mm$

Thus, the difference in the dimensions of the height of the dose-loading spacer guide and the height of the dose-delivery ring guide for a syringe with inner dimension 4.6 mm and for the loading and delivery of a dose of 7.5 μL was calculated to be 0.45 mm.

**[00030]** As can be seen from Figure 4, the dose-delivery guide can be shaped as a ring or cylinder, or it can have any shape of predetermined dimension. In use, the guide is placed on the syringe, typically at the "top" or proximal end. In the specific example shown in Figure 4, the guide can be placed around the plunger rod of the syringe (Fig. 4A). In Figure 4, the dose-delivery guide's inner dimension (I.D.) is slightly larger than the outer dimension (O.D.) of the plunger, such that the guide can move freely along the length of the plunger. In other words, in Figure 4, the plunger moves through the dose-delivery guide. In the specific embodiment shown in Figure 4, the dose-delivery guide is a continuous metal "ring," and can be placed on the plunger before the plunger is engaged with the syringe, or before or after the syringe is loaded. Alternatively, the dose-delivery guide may have an opening on the circumference to allow it to deform and "snap on" an extended plunger, substantially surrounding the plunger so that it may be released by the user and maintain its position along the plunger. The dose-delivery guide can be removeable or permanent.

**[00031]** The guide can be used without or with the dose-loading spacer described herein. In a particular embodiment, the dose-delivery guide is configured to fit snuggly into the opening of the dose-loading spacer guide (Fig. 4B). Alternatively, the dose-loading spacer is configured to abut either end of the dose-delivery guide.

**[00032]** In use, the dose-delivery guide is placed on the syringe either before or after the syringe is loaded with fluid. The amount of fluid loaded may be determined in traditional fashion (e.g., by visual inspection), without use of a dose-loading spacer. In this circumstance, the dose-delivery guide is advantageous when the syringe is somewhat deformeable, such that the dose delivery guide adds stability and thus better control over the dose delivered.

**[00033]** When used with the dose-loading spacer, the dose-delivery guide is placed on the syringe either before or after the syringe is loaded with fluid; the syringe is loaded with excess fluid; the dose-loading guide spacer is placed over/against the dose-delivery guide; the plunger is depressed until the dose-loading spacer stops the motion of the plunger, expelling excess fluid; the dose-loading guide is removed; the syringe needle is placed where the fluid is to be delivered; the plunger is depressed until the dose-delivery guide stops the motion of the plunger, delivering the fluid (e.g., administering the medication). In other words, the plunger travels along the length of the syringe barrel from point A to point B, the distance between point A

and B is directly related to the height of the dose-loading spacer and the height of the dose-delivery guide, and related to the volume (dose) to be delivered by the syringe.

**[00034]** Referring to Figure 5, this embodiment illustrates a system of a dual dose-loading spacer (Fig. 5A) configured for use with a dose-delivery guide (Fig. 5B). This example was designed for use with a BD 0.5 cc Hypak™ glass syringe with a BD PrecisionGlide™ 27 G ½" needle to deliver a dose of 7.5 μL. In this example, the syringe has a depression at the proximal end in which the dose-delivery guide inserts 0.6 mm. Thus, the dimensions of the dose-delivery guide has a longer height than that of the dose-loading guide, 8.01 mm compared to 7.86 mm spacer, respectively, to account for the depression in the syringe and still guide the accurate delivery of a 7.5 μL dose.

**[00035]** The dose-loading guide, dose-delivery guide, and the dual guide system (dose-loading/dose-delivery guides) of the present invention are particularly useful in circumstances where precise volumes of medication or sample are required. For example, delivery of a precise volume can be important when a pharmaceutical is very active such that a small amount results in significant biological activity (such as insulin); or where a pharmaceutical may have side-effects if a non-precise volume is delivered; or where the site of administration is small, such as in the eye (for example, IBI-20089, IBI-10090, LUCENTIS® ranibizumab injection, AVASTIN® bevacizumab, or VEGF Trap-Eye).

**[00036]** The dose-loading guide, dose-delivery guide or dual guide system of the present invention may also be included in a kit. The kit may include at least one guide or dual guide system; ,or may include a first guide or dual guide system for loading a first dose unit, and a second guide or second dual guide system for loading a second dose unit volume, etc. The kit may include at least one syringe for use with the guide or dual guide system. The kit may include a pharmaceutical or other active agent, a standard (e.g., for use with analytical detection), or materials for user practice (e.g., saline). The pharmaceutical may be preloaded into the syringe, e.g., excess pharmaceutical has been preloaded into the barrel of the syringe.

## EXAMPLES

Example 1. Improvement of small volume syringe-loading accuracy with dose-loading spacer

**[00037]** This example was designed to determine the standard deviation of using a 28 gauge syringe to deliver 7.5 μL of a sustained release composition (IBI-10090, having a density of ~1.15 mg/μL), with or without a dose-loading "spacer" guide.

**[00038]** Four people were given ten commercial insulin syringes (28 gauge); for each syringe, about 10 μL was drawn directly from a sample vial. Excess sample was expressed until approximately 7.5 μL was retained in the syringe as determined visually (i.e., by "eyeballing"

the correct unit volume). The unit volume was then injected into a tared vial and the weight recorded. This was repeated for all ten syringes.

**[00039]** The same four people then withdrew about 10 μL of sample and expressed the excess volume with the aid of the removable dose-loading guide as described herein until approximately 7.5 μL was retained in the syringe as determined by the collar portion of the dose-loading guide. The unit volume was then injected into a tared vial and the weight recorded. This was repeated for all ten syringes. The data are shown in Table 1:

Table 1. Comparative accuracy of syringe loading, dosing, without or with guide

| | without dose-loading guide | | | | with removable dose-loading guide | | | |
|---|---|---|---|---|---|---|---|---|
| User | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| Syringe | (mg) | (mg) | (mg) | (mg) | (mg) | (mg) | (mg) | (mg) |
| 1 | 7.23 | 10.85 | 9.47 | 7.76 | 9.52 | 9.50 | 9.55 | 8.15 |
| 2 | 7.54 | 10.11 | 7.06 | 9.56 | 9.62 | 9.94 | 9.01 | 8.18 |
| 3 | 7.47 | 9.50 | 9.36 | 10.09 | 8.93 | 9.37 | 8.25 | 9.08 |
| 4 | 8.47 | 9.96 | 13.36 | 6.12 | 9.60 | 8.44 | 7.70 | 8.30 |
| 5 | 7.10 | 10.11 | 12.43 | 9.85 | 8.70 | 8.55 | 8.48 | 8.89 |
| 6 | 9.23 | 11.20 | 7.94 | 10.47 | 8.48 | 7.63 | 9.07 | 8.15 |
| 7 | 9.54 | 8.51 | 10.42 | 8.99 | 9.20 | 8.10 | 8.06 | 7.89 |
| 8 | 8.32 | 8.45 | 10.28 | 10.06 | 9.75 | 8.12 | 8.74 | 8.06 |
| 9 | 9.19 | 11.94 | 10.72 | 8.99 | 8.43 | 8.15 | 9.62 | 8.39 |
| 10 | 9.09 | 10.06 | 11.53 | 7.30 | 8.79 | 9.23 | 7.75 | 8.11 |
| | Average weight (mg) 9.39 | | | | Average weight (mg) 8.68 | | | |
| | SD 1.57 | | | | SD 0.63 | | | |
| | RSD 16.68 | | | | RSD 7.28 | | | |
| | | | | | | | | |
| | Average volume (μL) 8.17 | | | | Average volume (μL) 7.48 | | | |
| | SD 1.36 | | | | SD 0.55 | | | |
| | RSD 16.68 | | | | RSD 7.35 | | | |

**[00040]** As can be seen from the data in Table 1, significant accuracy was achieved by using the dose-loading spacer device.

**[00041]** In several additional experiments using the removable dose-loading guide, syringes were loaded with a pharmaceutical composition using the guide, and accuracy was demonstrated as shown in Table 2:

Table 2. Accuracy of 300 guided 7.5 μL doses

| # syringes | # users | Total | ave mg | ave μL |
|---|---|---|---|---|
| 10 | 10 | 100 | 8.72 ± 1.05 | 7.58 ± 0.91 |
| 10 | 10 | 100 | 8.454 ± 0.79 | 7.43 ± 0.69 |
| 10 | 10 | 100 | 8.55 ± 0.68 | 7.50 ± 0.59 |

**[00042]** A further set of data was collected using water, as shown in Table 3:

Table 3. Accuracy of 100 guided 7.5 µL doses

| # syringes | # users | Total | ave mg | avc µL |
|---|---|---|---|---|
| 10 | 10 | 100 | 7.53 ± 0.44 | 7.53 ± 0.44 |

Example 2. Dual dose-loading/dose-delivery guide system

**[00043]** In early experiments, using a 8.45 mm dose-loading spacer and a 8.00 mm dose-delivery ring with the BD 0.5 cc Hypak™ glass syringe attached with a BD PrecisionGlide™ 27 G ½" needle, the volume delivered was higher than the expected 7.5 µL. After careful examination of the BD Hypak™ syringe, it was found that the flange of the proximal end of the syringe, where the plunger rod enters the syringe barrel, is not perfectly flat; but rather it has a 0.6 mm depression or groove in which the delivery-guide actually seats into or sinks in. The dimensions of the dose-loading guide and the dose-delivery guide were then re-designed to make a 7.85 mm spacer and corresponding 8.0 mm ring, which resulted in the more accurate delivery of a ~7.5 µL dose. Table 4 shows data compiled using this dual guide system for a fluid having a density of 1.16 gm/mL (1.16 mg/µL), such that 8.62 mg/1.16 mg/µL = 7.43 µL.

Table 4. Delivery of 7.5 µL using dual dose-loading dose-delivery guide system

| | Syringe # | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | | |
| | 9.10 | 8.89 | 8.65 | 8.27 | 8.27 | 9.37 | 8.71 | | |
| | 9.18 | 8.69 | 9.16 | 8.20 | 8.90 | 9.69 | 7.29 | | |
| | 8.55 | 8.22 | 9.17 | 7.98 | 8.57 | 9.99 | 7.91 | | |
| | 8.38 | 8.54 | 8.94 | 8.70 | 8.79 | 8.92 | 8.37 | | |
| | 9.96 | 9.03 | 8.99 | 8.34 | 8.58 | 9.33 | 8.06 | | |
| | 8.44 | 8.35 | 8.62 | 8.32 | 8.67 | 9.20 | 6.89 | | |
| | 8.88 | 8.71 | 9.02 | 8.56 | 8.32 | 8.56 | 7.28 | | |
| | 8.85 | 8.41 | 9.11 | 8.65 | 8.89 | 8.41 | 7.98 | | |
| | 8.97 | 8.08 | 8.44 | 8.20 | 8.79 | 7.93 | 7.87 | | |
| | 9.12 | 8.80 | 8.88 | 8.18 | 8.47 | 9.42 | 8.50 | **Weight (mg)** | **Volume (µL)** |
| Average | 8.94 | 8.57 | 8.90 | 8.34 | 8.63 | 9.08 | 7.89 | **8.62** | **7.43** |
| SD | 0.46 | 0.31 | 0.25 | 0.23 | 0.22 | 0.63 | 0.58 | 0.55 | 0.47 |
| RD | 5.12 | 3.56 | 2.81 | 2.75 | 2.59 | 6.91 | 7.38 | 6.39 | 6.39 |

CLAIMS

We claim:

1. A removable dose-loading guide for loading an injection syringe comprising a grip portion and a collar portion, the collar portion designed to be removably placed at the proximal end of a syringe barrel abutting an extended syringe plunger rod ; wherein the collar is rigid and includes an opening for removably receiving the extended syringe plunger, and whose inner wall bears against the plunger rod for guided displacement therealong, and wherein the collar portion has predetermined dimensions and, in use, stops the movement of the plunger into the syringe barrel at a predetermined distance from the syringe barrel, which distance is directly related to the volume to be delivered by the injection syringe.

2. The guide of claim 1, wherein the dose-loading guide bears an indication of the dose volume it is used to deliver.

3. A dose-delivery guide for loading and dispensing fluid from an injection syringe, wherein said dose-delivery guide is designed to be placed, removably or permanently, abutting an extended syringe plunger rod for guided displacement therethrough, wherein the dose-delivery guide is rigid along its height and has predetermined dimensions and, in use, stops the movement of the plunger into the barrel of the syringe at a predetermined distance from the syringe barrel, which distance is related directly to the volume to be expelled from the injection syringe.

4. The dose-delivery guide of claim 3, wherein the dose-delivery guide bears an indication of the dose volume it is used to deliver.

5. The dose-delivery guide of claim 3 or 4, wherein said guide is configured for use with a BD 0.5 cc Hypak™ glass syringe.

6. The dose-delivery guide of claim 5, wherein said guide is integral to the plunger.

7. A dual dose-loading dose-delivery guide system for loading and dispensing an injection syringe comprising (a) a dose-delivery guide designed to be placed, removably or permanently, on an extended syringe plunger rod for guided displacement therethrough, wherein the dose-delivery guide is rigid along its height and has predetermined dimensions and, in use, stops the movement of the plunger into the syringe barrel at a predetermined distance from the syringe barrel, which distance is related to the volume to be expelled from the injection syringe.; and (b) a removable dose-loading guide comprising a grip portion and a collar portion, the collar portion designed to be removably placed against the dose-delivery guide; wherein the collar is rigid and includes an opening for removably receiving the dose-delivery guide, and whose inner wall bears against the dose-delivery guide for guided displacement therealong, and wherein the

collar has predetermined dimensions and, in use, stops the movement of the plunger into the syringe barrel at a predetermined distance from the syringe barrel, which distance is related to the volume to be retained in the injection syringe.

8. A kit comprising the dose-loading guide of claim 1 or 2, the dose-delivery guide of claims 3-6, or the dual dose-loading dose-delivery guide system of claim 7.

9. The kit of claim 8, further comprising at least one syringe.

10. The kit of claim 9, wherein the syringe is a 100cc insulin syringe.

11. The kit of claim 9, wherein the syringe is a BD 0.5 cc Hypak™ glass syringe.

12. The kit of claim 11, wherein the dose-delivery guide is integral to the plunger of said syringe.

13. The kit of any one of claims 9-12, further comprising a pharmaceutical composition.

14. The kit of claim 13, wherein the pharmaceutical is insulin.

15. The kit of claim 13, wherein the pharmaceutical composition is IBI-20089.

16. The kit of claim 13, wherein the pharmaceutical composition is LUCENTIS®, AVASTIN®, or VEGF Trap-Eye.

17. The kit of claim 13, wherein the pharmaceutical composition is an opioid.

18. The kit of claim 13, wherein the pharmaceutical composition is IBI-10090.

19. The kit of any one of claims 13-18, wherein the pharmaceutical composition is preloaded in a syringe.

20. The kit of any one of claims 8-19, further comprising instructions for using the dose-loading guide, the dose-delivery guide, or the dual dose-loading dose-delivery guide system.

21. A method of using the dual dose-loading dose-delivery system of claim 7, comprising drawing an excess of fluid into a syringe bearing the dose-delivery guide; placing the collar portion of the dose-loading guide against the dose-delivery guide; depressing the plunger until the dose-loading guide stops the motion of the plunger; and removing the dose-loading guide.

22. The method of claim 21, further comprising the step of depressing the plunger until the dose-delivery guide stops the motion of the plunger.

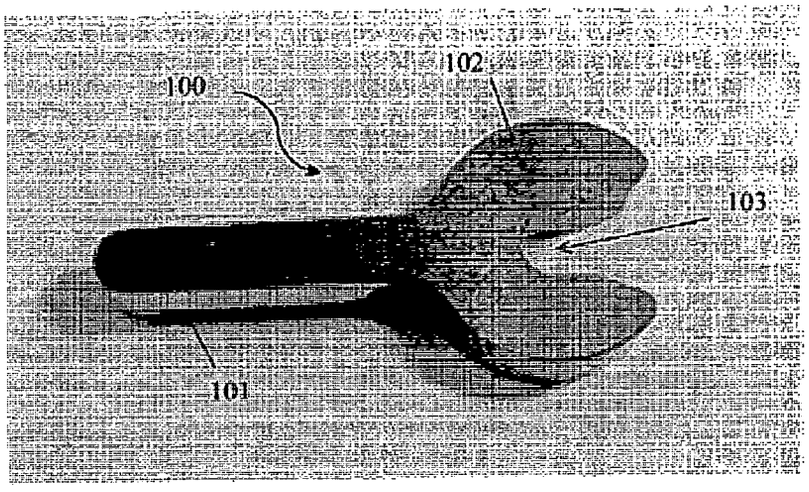


Figure 1A

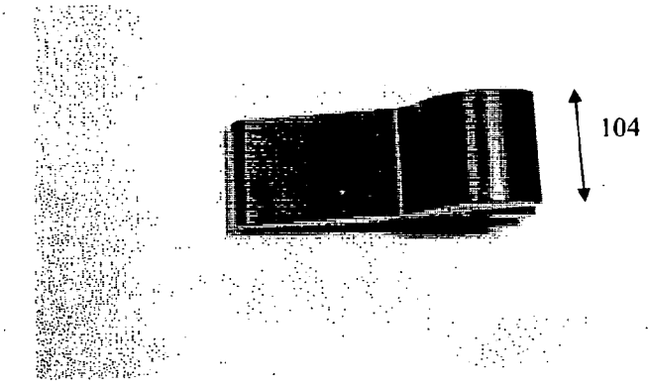


Figure 1B

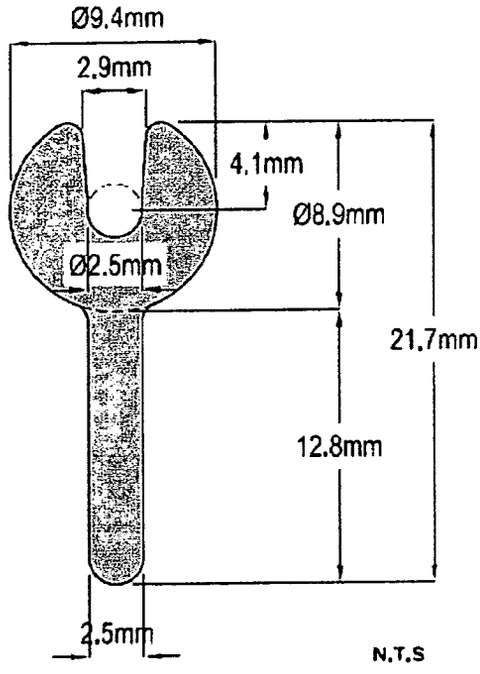


Figure 2A

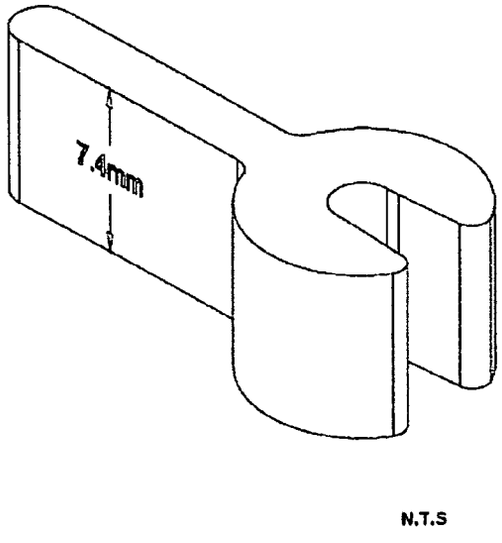


Figure 2B

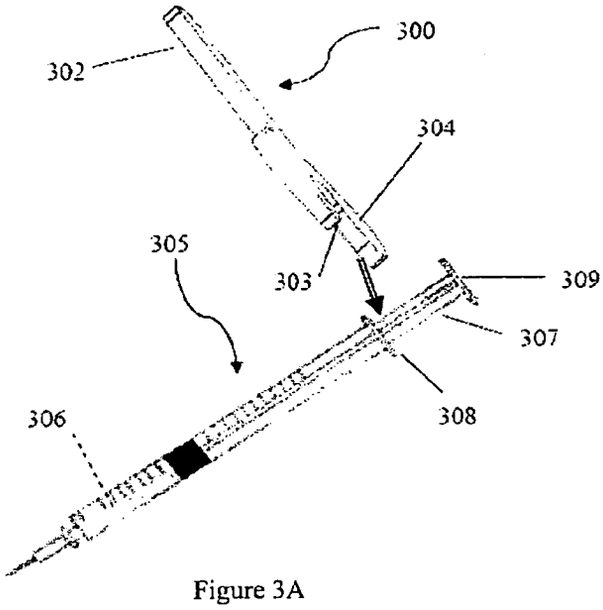


Figure 3A

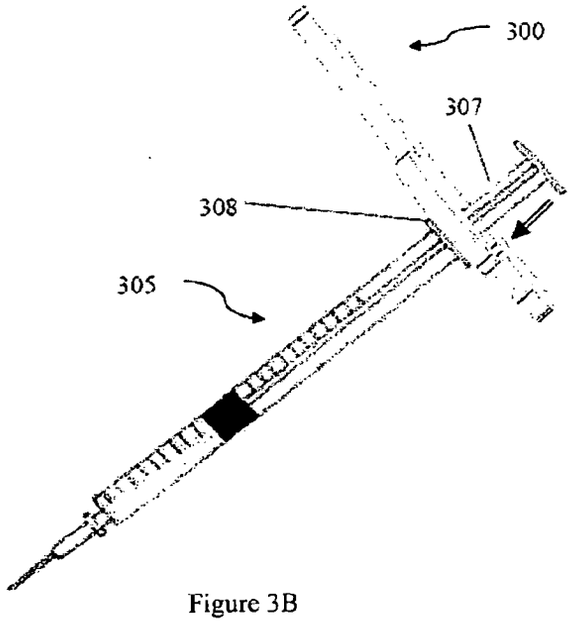


Figure 3B

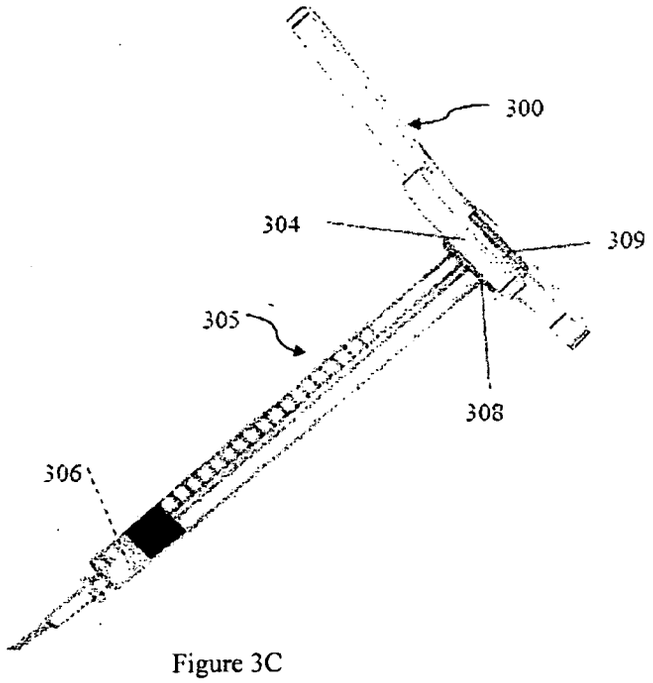


Figure 3C

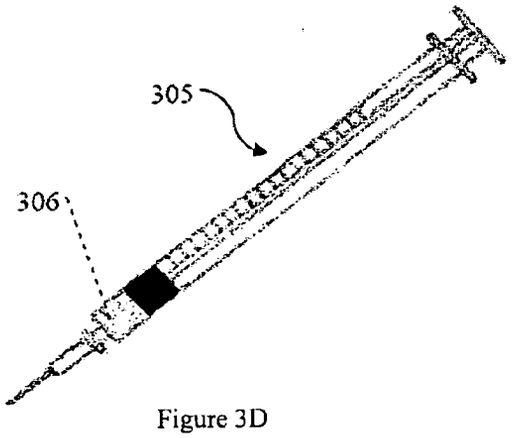


Figure 3D

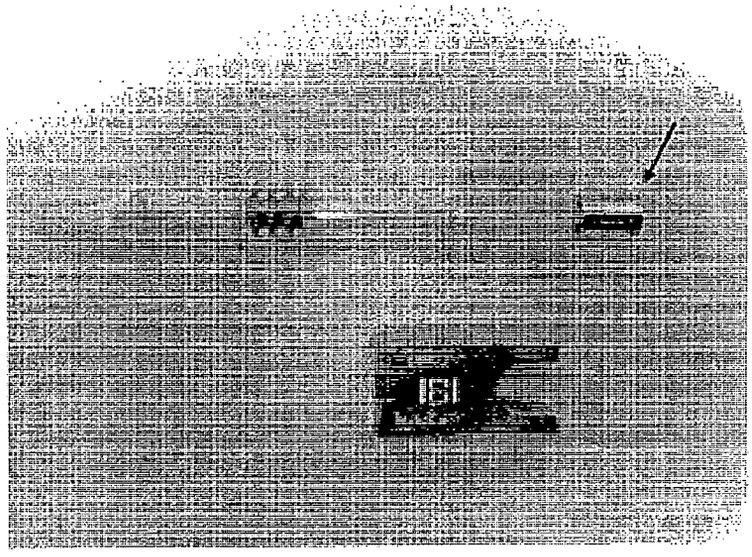

Figure 4A

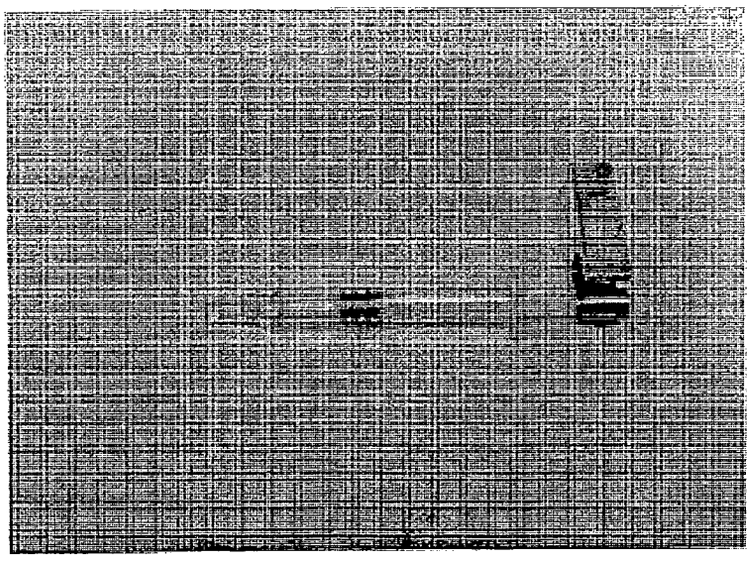

Figure 4B

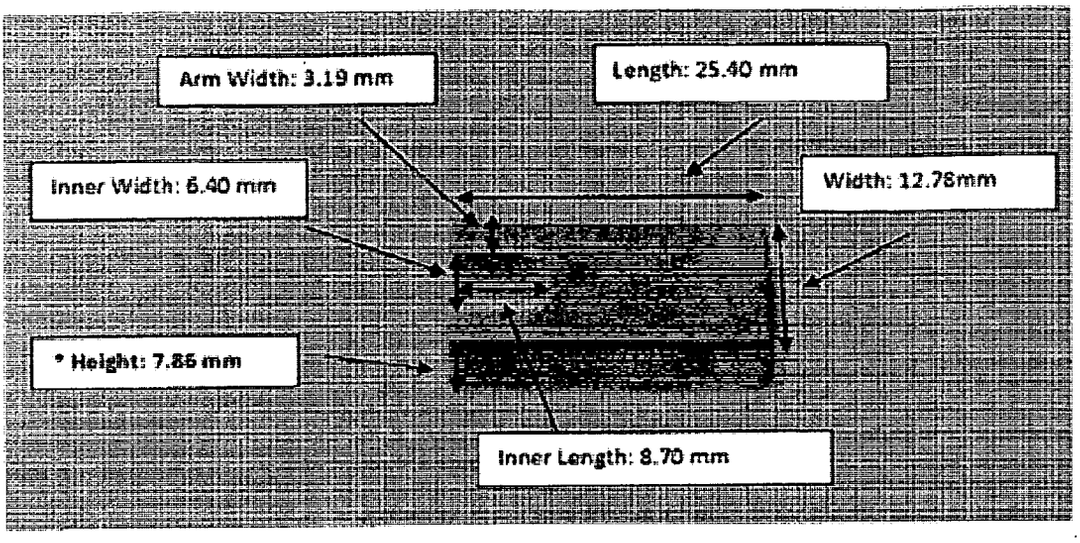


Figure 5A

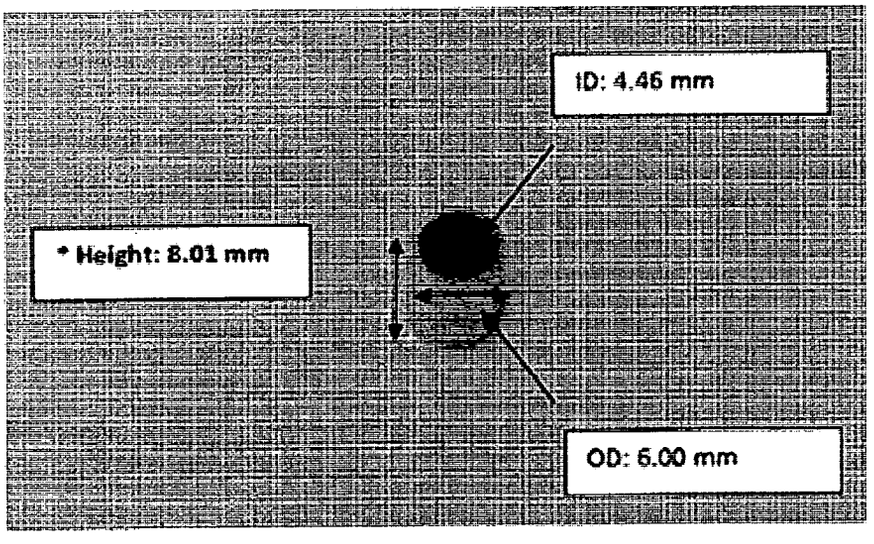


Figure 5B

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(54) Title: VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION

(57) Abstract: Ophthalmic formulations of a vascular endothelial growth factor (VEGF)-specific fusion protein antagonist are provided suitable for intravitreal administration to the eye. The ophthalmic formulations include a stable liquid formulation and a lyophilizable formulation. Preferably, the protein antagonist has the amino acid sequence shown in SEQ ID NO:4.

WO 2007/149334 A2

# VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION

## BACKGROUND OF INVENTION

### Field of the Invention

**[0001]** The present invention is directed to pharmaceutical formulations suitable for intravitreal administration comprising agents capable of inhibiting vascular endothelial growth factor (VEGF), and to methods for making and using such formulations. The invention includes liquid pharmaceutical formulations having increased stability, as well as formulations that may be lyophilize and reconstituted for intravitreal administration.

### Statement of Related Art

**[0002]** Vascular endothelial growth factor (VEGF) expression is nearly ubiquitous in human cancer, consistent with its role as a key mediator of tumor neoangiogenesis. Blockade of VEGF function, by binding to the molecule or its VEGFR-2 receptor, inhibits growth of implanted tumor cells in multiple different xenograft models (see, for example, Gerber et al. (2000) Cancer Res. 60:6253-6258). A soluble VEGF-specific fusion protein antagonist, termed a "VEGF trap" has been described (Kim et al. (2002) Proc. Natl. Acad. Sci. USA 99:11399-404; Holash et al. (2002) Proc. Natl. Acad. Sci. USA 99:11393-8).

**[0003]** Ophthalmic formulations are known, see for example, U.S. 7,033,604 and 6,777,429. An ophthalmic formulation of a VEGF antibody is described in US 6,676,941.

**[0004]** Lyophilization (freeze drying under controlled conditions) is commonly used for long-term storage of proteins. The lyophilized protein is substantially resistant to degradation, aggregation, oxidation, and other degenerative processes while in the freeze-dried state (see, for example, U.S. 6,436,897).

## BRIEF SUMMARY OF THE INVENTION

**[0005]** Stable formulations of a VEGF-specific fusion protein antagonist are provided. Pharmaceutically acceptable formulations are provided that comprise a VEGF "trap" antagonist with a pharmaceutically acceptable carrier. In specific embodiments, liquid and lyophilized formulations are provided.

**[0006]** In a first aspect, a stable liquid ophthalmic formulation of a VEGF-specific fusion protein antagonist is provided, comprising a fusion protein that comprises a receptor component consisting essentially of an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component (also termed a "VEGF trap"). In a specific embodiment of the VEGF-specific fusion protein antagonist, the first VEGF receptor is Flt1 and the second VEGF receptor is Flk1 or Flt4. In a more specific embodiment the fusion protein has the amino acid sequence of SEQ ID NO:2 or SEQ ID NO:4. Preferably,

the VEGF antagonist is a dimer comprising two fusion proteins of SEQ ID NO:4.

**[0007]** In one aspect, a stable liquid ophthalmic formulation is provided that comprises 1-100 mg/ml VEGF-specific fusion protein antagonist, 0.01-5% of one or more organic co-solvent(s), 30-150 mM of one or more tonicity agent(s), 5-40 mM of a buffering agent, and optionally, 1.0-7.5% of a stabilizing agent, pH between about 5.8-7.0.

**[0008]** In one or more specific embodiments, the organic co-solvent may be polysorbate, for example, polysorbate 20 or polysorbate 80, polyethylene glycol (PEG), for example, PEG 3350, or propylene glycol, or a combination thereof; the tonicity agent may be, for example, sodium chloride or potassium chloride; the stabilizing agent may be sucrose, sorbitol, glycerol, trehalose, or mannitol; and the buffering agent may be, for example, phosphate buffer. In a specific embodiment, the phosphate buffer is a sodium phosphate buffer.

**[0009]** In various embodiments, the organic co-solvent is polysorbate and/or PEG, the stabilizing agent is sucrose, the buffering agent is phosphate buffer, and the tonicity agent is sodium chloride.

**[0010]** More specifically, the stable liquid ophthalmic formulation comprises about 40-50 mg/ml of the VEGF antagonist (SEQ ID NO:4), about 10 mM phosphate buffer, 0.01-3% polysorbate and/or PEG, 40-135 mM sodium chloride, and optionally 5.0% sucrose, pH about 6.2-6.3.

**[0011]** In a specific preferred embodiment, the stable liquid ophthalmic formulation comprises about 50 mg/ml of the VEGF antagonist (SEQ ID NO:4), 10 mM sodium phosphate buffer, 50 mM sodium chloride, 0.1% polysorbate, and 5% sucrose, pH about 6.2-6.3.

**[0012]** In a specific preferred embodiment, the stable liquid ophthalmic formulation comprises about 50 mg/ml of the VEGF antagonist (SEQ ID NO:4), 10 mM sodium phosphate buffer, 50 mM sodium chloride, 3% PEG, and 5% sucrose, pH about 6.2-6.3.

**[0013]** In a specific preferred embodiment, the stable liquid ophthalmic formulation comprises about 40 mg/ml of the VEGF antagonist (SEQ ID NO:4), 10 mM sodium phosphate buffer, 40 mM sodium chloride, 0.03% polysorbate, and 5% sucrose, pH about 6.2-6.3.

**[0014]** In a specific preferred embodiment, the stable liquid ophthalmic formulation comprises about 40 mg/ml of the VEGF antagonist (SEQ ID NO:4), 10 mM sodium phosphate buffer, 135 mM sodium chloride, and 0.03% polysorbate, pH about 6.2-6.3.

**[0015]** In another aspect, a stable liquid ophthalmic formulation is provided that comprises 1-100 mg/ml VEGF-specific fusion protein antagonist; 0.01-5% of one or more organic co-solvent(s); 5-40 mM of a buffering agent; and optionally 30-150 mM of one or more tonicity agent(s) and/or 1.0-7.5% of a stabilizing agent; having a pH between about 5.8-7.0.

**[0016]** In various embodiments, the VEGF antagonist (SEQ ID NO:4) is present at a concentration of about 10 to about 80 mg/ml. In various embodiments, the VEGF antagonist (SEQ ID NO:4) is present at a concentration of about 10, about 20, about 30, about 40, about 50, about 60, about 70, or about 80 mg/ml. In a preferred embodiment, the VEGF antagonist

(SEQ ID NO:4) is present at a concentration of about 40 mg/ml.

**[0017]** In another embodiment, the stabilizing agent is selected from one or more of sucrose, sorbitol, glycerol, trehalose, and mannitol.

**[0018]** In another embodiment, the organic co-solvent is selected from one or more of polysorbate, for example, polysorbate 20 or polysorbate 80, polyethylene glycol (PEG), for example, PEG 3350, and propylene glycol.

**[0019]** In another embodiment, the buffer is a phosphate buffer, for example, sodium phosphate.

**[0020]** In another embodiment, the tonicity agent is a salt, for example, sodium chloride.

**[0021]** In one embodiment, the stable liquid ophthalmic formulation comprises 10 mM sodium phosphate buffer, about 0.03 to about 0.1% polysorbate and/or about 3% PEG or propylene glycol, about 40 mM sodium chloride, and about 5% sucrose. In a specific embodiment, the stable liquid ophthalmic formulation comprises 10 mM sodium phosphate buffer, about 0.03% polysorbate, about 40 mM sodium chloride, and about 5% sucrose. In another specific embodiment, the pH of the formulation is about 6.2 to about 6.3. In another specific embodiment, the pH is achieved by mixing mono- and dibasic sodium phosphate to the desired pH without acid/base titration.

**[0022]** In a specific embodiment, the stable liquid ophthalmic formulation consists essentially of a VEGF antagonist (SEQ ID NO:4) at 40 mg/ml, 10 mM sodium phosphate buffer, polysorbate at 0.03%, sodium chloride at 40 mM, and sucrose at 5%, pH 6.2-6.3.

**[0023]** In another aspect, a stable liquid ophthalmic formulation is provided that comprises about 10 to about 80 mg/ml VEGF antagonist, about 10 mM sodium phosphate buffer, about 0.03% polysorbate, and about 135 mM sodium chloride, pH of 6.2 to 6.3.

**[0024]** In various embodiments, the VEGF antagonist (SEQ ID NO:4) is present at a concentration of about 10 to about 80 mg/ml. In various embodiments, the VEGF antagonist (SEQ ID NO:4) is present at a concentration of about 10, about 20, about 30, about 40, about 50, about 60, about 70, or about 80 mg/ml. In a specific embodiment, the VEGF antagonist (SEQ ID NO:4) is present at a concentration of about 40 mg/ml.

**[0025]** In one embodiment, the stable liquid ophthalmic formulation comprises 40 mg/ml of VEGF antagonist (SEQ ID NO:4), 10 mM sodium phosphate buffer, 0.03% polysorbate, and 135 mM sodium chloride at pH 6.2-6.3. In a specific embodiment, the stable liquid ophthalmic formulation consists essentially of 40 mg/ml of VEGF antagonist (SEQ ID NO:4), 10 mM sodium phosphate buffer, 0.03% polysorbate, and 135 mM sodium chloride at pH 6.2-6.3.

**[0026]** In another aspect, a lyophilizable formulation of a VEGF antagonist is provided, wherein upon lyophilization followed by reconstitution, a stable liquid ophthalmic formulation as described herein is obtained.

**[0027]** In another aspect, a lyophilizable formulation of a vascular endothelial growth factor

(VEGF)-specific fusion protein antagonist is provided, comprising 5-50 mg/ml of the VEGF antagonist, 5-25 mM buffer, such as phosphate buffer, 0.01 to 0.15% of one or more of an organic co-solvent, such as polysorbate, propylene glycol and/or PEG, and optionally 1-10% of a stabilizing agent such as sucrose, sorbitol, trehalose, glycerol, or mannitol, pH about 5.8-7.0. In various embodiments, the VEGF antagonist (SEQ ID NO:4) is present at about 5, about 10, about 20, about 30, or about 40 mg/ml. In a specific embodiment, the lyophilizable ophthalmic formulation of the invention comprises 20 mg/ml of the VEGF antagonist, 10 mM sodium phosphate buffer, 0.03% polysorbate, 0.1% PEG, and 2.5% sucrose, pH about 6.2-6.3. In further embodiments, the lyophilizable formulation further comprises sodium chloride. In a specific embodiment, the sodium chloride is present at a concentration of about 20 mM. In another specific embodiment, the sodium chloride is present at a concentration of about 67.5 mM.

**[0028]** In another specific embodiment, the lyophilizable ophthalmic formulation of the invention comprises 20 mg/ml of the VEGF antagonist, 5 mM sodium phosphate buffer, 0.015% polysorbate, 20 mM sodium chloride, and 2.5% sucrose, pH about 6.2-6.3.

**[0029]** In another embodiment, the lyophilizable ophthalmic formulation comprises 5 mg/ml, 10 mg/ml, or 40 mg/ml VEGF antagonist, 5 mM sodium phosphate buffer, 0.015% polysorbate, 20 mM sodium chloride, and 2.5% sucrose, at pH 6.2-6.3. In a specific embodiment, the lyophilizable ophthalmic formulation consists essentially of 5 mg/ml, 10 mg/ml, or 40 mg/ml VEGF antagonist (SEQ ID NO:4), 5 mM sodium phosphate buffer, 0.015% polysorbate, 20 mM sodium chloride, and 2.5% sucrose, at pH 6.2-6.3.

**[0030]** In another specific embodiment, the lyophilizable ophthalmic formulation comprises 20 mg/ml of the VEGF antagonist, 5 mM sodium phosphate buffer, 0.015% polysorbate, and 67.5 mM sodium chloride, pH about 6.2-6.3. In a more specific embodiment, the lyophilizable ophthalmic formulation consists essentially of 20 mg/ml of the VEGF antagonist (SEQ ID NO:4), 5 mM sodium phosphate buffer, 0.015% polysorbate, and 67.5 mM sodium chloride, pH 6.2-6.3.

**[0031]** In another specific embodiment, the lyophilizable ophthalmic formulation comprises 5 mg/ml, 10 mg/ml, or 40 mg/ml VEGF antagonist, 5 mM sodium phosphate buffer, 0.015% polysorbate, and 67.5 mM sodium chloride, pH about 6.2-6.3. In a more specific embodiment, the lyophilizable ophthalmic formulation consists essentially of 5 mg/ml, 10 mg/ml, or 40 mg/ml VEGF antagonist (SEQ ID NO:4), 5 mM sodium phosphate buffer, 0.015% polysorbate, and 67.5 mM sodium chloride, pH about 6.2-6.3.

**[0032]** Generally, the reconstituted formulation is about 2 times the concentration of the pre-lyophilized formulation, e.g., a 20 mg fusion protein/ml pre-lyophilized formulation is reconstituted to a final formulation of 40 mg fusion protein/ml.

**[0033]** Generally, the lyophilized formulation is reconstituted with sterile water suitable for injection. In one embodiment, the reconstitution liquid is bacteriostatic water.

[0034] In another aspect, the invention features a method of producing a lyophilized formulation of a VEGF-specific fusion protein antagonist, comprising subjecting the lyophilizable formulation of the invention to lyophilization to generate a lyophilized formulation. The lyophilized formulation may be lyophilized by any method known in the art for lyophilizing a liquid.

[0035] In another related aspect, the invention features a method of producing a reconstituted lyophilized formulation of a VEGF antagonist, comprising reconstituting the lyophilized formulation of the invention to a reconstituted formulation. In one embodiment, the reconstituted formulation is twice the concentration of the pre-lyophilized formulation, e.g., the method of the invention comprises: (a) producing a pre-lyophilized formulation of a VEGF-specific fusion protein antagonist, (b) subjecting the pre-lyophilized formulation of step (a) to lyophilization; and (c) reconstituting the lyophilized formulation of step (b).

[0036] The invention further features ophthalmic formulations provided in a pre-filled syringe or vial, particularly suitable for intravitreal administration.

[0037] Other objects and advantages will become apparent from a review of the ensuing detailed description.

## DETAILED DESCRIPTION OF THE INVENTION

[0038] The present invention is not limited to particular methods, and experimental conditions described, as such methods and conditions may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting unless indicated, since the scope of the present invention will be limited only by the appended claims.

[0039] Unless stated otherwise, all technical and scientific terms and phrases used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are now described.

### General Description

[0040] Safe handling and administration of formulations comprising proteins represent significant challenges to pharmaceutical formulators. Proteins possess unique chemical and physical properties that present stability problems: a variety of degradation pathways exist for proteins, implicating both chemical and physical instability. Chemical instability includes deamination, aggregation, clipping of the peptide backbone, and oxidation of methionine residues. Physical instability encompasses many phenomena, including, for example, aggregation and/or precipitation.

[0041] Chemical and physical stability can be promoted by removing water from the protein.

Lyophilization (freeze-drying under controlled conditions) is commonly used for long-term storage of proteins. The lyophilized protein is substantially resistant to degradation, aggregation, oxidation, and other degenerative processes while in the freeze-dried state. The lyophilized protein may be reconstituted with water optionally containing a bacteriostatic preservative (e.g., benzyl alcohol) prior to administration.

**Definitions**

**[0042]** The term "carrier" includes a diluent, adjuvant, excipient, or vehicle with which a composition is administered. Carriers can include sterile liquids, such as, for example, water and oils, including oils of petroleum, animal, vegetable or synthetic origin, such as, for example, peanut oil, soybean oil, mineral oil, sesame oil and the like.

**[0043]** The term "excipient" includes a non-therapeutic agent added to a pharmaceutical composition to provide a desired consistency or stabilizing effect. Suitable pharmaceutical excipients include, for example, starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like.

**[0044]** The term "lyophilized" or "freeze-dried" includes a state of a substance that has been subjected to a drying procedure such as lyophilization, where at least 90% of moisture has been removed.

**VEGF Antagonists**

**[0045]** A VEGF antagonist is a compound capable of blocking or inhibiting the biological action of vascular endothelial growth factor (VEGF), and includes fusion proteins capable of trapping VEGF. In a preferred embodiment, the VEGF antagonist is the fusion protein of SEQ ID NO:2 or 4; more preferably, SEQ ID NO:4. In specific embodiments, the VEGF antagonist is expressed in a mammalian cell line such as a CHO cell and may be modified post-translationally. In a specific embodiment, the fusion protein comprises amino acids 27-457 of SEQ ID NO:4 and is glycosylated at Asn residues 62, 94, 149, 222 and 308. Preferably, the VEGF antagonist is a dimer composed of two fusion proteins of SEQ ID NO:4.

**[0046]** The VEGF antagonist of the methods and formulations of the invention can be prepared by any suitable method known in the art, or that comes to be known. The VEGF antagonist is preferably substantially free of protein contaminants at the time it is used to prepare the pharmaceutically acceptable formulation. By "substantially free of protein contaminants" is meant, preferably, that at least 90 % of the weight of protein of the VEGF-specific fusion protein antagonist preparation used for making a formulation is VEGF fusion protein antagonist protein, more preferably at least 95%, most preferably at least 99%. The fusion protein is preferably substantially free of aggregates. "Substantially free of aggregates" means that at least 90% of

the weight of fusion protein is not present in an aggregate at the time the fusion protein is used to prepare the pharmaceutically effective formulation. Unless stated otherwise, the phosphates employed are sodium phosphates and a desired buffering pH is achieved by mixing appropriate amounts of mono- and dibasic sodium phosphate.

**Stable Liquid Ophthalmic Formulations**

**[0047]** In one aspect, the invention provides a stable pharmaceutically acceptable formulation comprising a VEGF antagonist, wherein the formulation is a liquid formulation suitable for ophthalmic use. Preferably, the liquid formulation comprises a pharmaceutically effective amount of the VEGF antagonist. The formulation can also comprise one or more pharmaceutically acceptable carriers, buffers, tonicity agents, stabilizers, and/or excipients. An example of a pharmaceutically acceptable liquid formulation comprises a VEGF antagonist in a pharmaceutically effective amount, a buffer, an organic co-solvent such as polysorbate, a tonicity agent such as NaCl, and optionally, a stabilizer such as sucrose or trehalose.

**[0048]** Stability is determined in a number of ways at specified time points, including determination of pH, visual inspection of color and appearance, determination of total protein content by methods known in the art, e.g., UV spectroscopy, and purity is determined by, for example, SDS-PAGE, size-exclusion HPLC, bioassay determination of activity, isoelectric focusing, and isoaspartate quantification. In one example of a bioassay useful for determining VEGF antagonist activity, a BAF/3 VEGFR1/EPOR cell line is used to determine VEGF165 binding by the VEGF antagonist of the invention.

**[0049]** Liquid formulations can be stored in an oxygen-deprived environment. Oxygen-deprived environments can be generated by storing the formulations under an inert gas such as, for example, nitrogen or argon. Liquid formulations are preferably stored at about 5°C.

**Ophthalmic Lyophilized Formulations**

**[0050]** In one aspect of the invention, an ophthalmically acceptable formulation comprising a VEGF antagonist is provided, wherein the formulation is a lyophilizable formulation. Lyophilizable formulations can be reconstituted into solutions, suspensions, emulsions, or any other suitable form for administration or use. Lyophilizable formulations are typically first prepared as liquids, then frozen and lyophilized. The total liquid volume before lyophilization can be less, equal to, or more than, the final reconstituted volume of the lyophilized formulation. The lyophilization process is well known to those of ordinary skill in the art, and typically includes sublimation of water from a frozen formulation under controlled conditions.

**[0051]** Lyophilized formulations can be stored at a wide range of temperatures. Lyophilized formulations may be stored below 25°C, for example, refrigerated at 2-8°C, or at room temperature (e.g., approximately 25°C). Preferably, lyophilized formulations are stored below

about 25°C, more preferably, at about 4-20°C; below about 4°C; below about -20°C; about -40°C; about -70°C, or about -80°C. Stability of the lyophilized formulation may be determined in a number of ways known to the art, for example, by visual appearance of the cake and/or by moisture content.

**[0052]** Lyophilized formulations are typically reconstituted for use by addition of an aqueous solution to dissolve the lyophilized formulation. A wide variety of aqueous solutions can be used to reconstitute a lyophilized formulation. Preferably, lyophilized formulations are reconstituted using water. Lyophilized formulations are preferably reconstituted with a solution consisting essentially of water (e.g., USP WFI, or water for injection) or bacteriostatic water (e.g., USP WFI with 0.9% benzyl alcohol). However, solutions comprising buffers and/or excipients and/or one or more pharmaceutically acceptable carries can also be used.

**[0053]** Freeze-dried or lyophilized formulations are typically prepared from liquids, that is, from solutions, suspensions, emulsions, and the like. Thus, the liquid that is to undergo freeze-drying or lyophilization preferably comprises all components desired in a final reconstituted liquid formulation. As a result, when reconstituted, the freeze-dried or lyophilized formulation will render a desired liquid formulation upon reconstitution.

## EXAMPLES

**[0054]** Before the present methods are described, it is to be understood that this invention is not limited to particular methods, and experimental conditions described, as such methods and conditions may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only to the appended claims.

**[0055]** Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are now described.

### Example 1. Stability of 50 mg/ml VEGF Trap Liquid Formulation Stored at 5° C in 3 ml Glass Vials.

**[0056]** An ophthalmic liquid formulation containing 50 mg/ml VEGF Trap (SEQ ID NO:4), 10 mM phosphate, 50 mM NaCl, 0.1% polysorbate 20, 5% sucrose, and pH 6.25, was stored at 5 °C in 3 ml glass vials and samples tested at 3, 6, 9, 12, 18 and 24 months. Stability was determined by SE-HPLC. The results are shown in Table 1. Turbidity was measured at $OD_{405}$ nm; and percent recovered protein and purity by size exclusion HPLC.

Table 1. Stability of 50 mg/ml VEGF Trap Protein (VGFT-SS065)

| Months | Visual Appearance | Turbidity ($OD_{405}$ nm) | pH | % VEGF Trap Recovered | % VEGF Trap Native Configuration |
|---|---|---|---|---|---|
| 0 | Pass | 0.00 | 6.2 | 100 | 98.8 |
| 3 | Pass | 0.00 | 6.2 | 101 | 98.7 |
| 6 | Pass | 0.01 | 6.3 | 100 | 98.3 |
| 9 | Pass | 0.01 | 6.3 | 101 | 98.3 |
| 12 | Pass | 0.01 | 6.3 | 104 | 98.4 |
| 18 | Pass | 0.01 | 6.3 | 96 | 98.1 |
| 24 | Pass | 0.01 | 6.3 | 105 | 98.1 |

**Example 2. Stability of 50 mg/ml VEGF Trap Liquid Formulation Stored at 5°C in 3 ml Glass Vials.**

**[0057]** A liquid formulation containing 50 mg/ml VEGF Trap (SEQ ID NO:4), 10 mM phosphate, 50 mM NaCl, 3% polyethylene glycol 3350, 5% sucrose, and pH 6.25, was stored at 5 °C in 3 nil glass vials and samples tested at 3, 6, 9, 12, 18 and 24 months. Stability results are shown in Table 2. Turbidity, percent recovered protein and purity was determined as described above.

Table 2. Stability of 50 mg/ml VEGF Trap Protein (VGFT-SS065)

| Months | Visual Appearance | Turbidity | pH | % VEGF Trap Recovered | % VEGF Trap Native Configuration |
|---|---|---|---|---|---|
| 0 | Pass | 0.00 | 6.2 | 100 | 98.9 |
| 3 | Pass | 0.00 | 6.1 | 104 | 98.5 |
| 6 | Pass | 0.01 | 6.3 | 99 | 98.3 |
| 9 | Pass | 0.00 | 6.3 | 102 | 97.6 |
| 12 | Pass | 0.01 | 6.3 | 103 | 98.0 |
| 18 | Pass | 0.00 | 6.3 | 113 | 97.7 |
| 24 | Pass | 0.00 | 6.2 | 106 | 97.6 |

**Example 3. Stability of 40 mg/ml VEGF Trap Liquid Formulation Stored at 5°C in 3 ml Glass Vials.**

**[0058]** A liquid formulation containing 40 mg/ml VEGF Trap (SEQ ID NO:4), 10 mM phosphate, 40 mM NaCl, 0.03% polysorbate 20, 5% sucrose, and pH 6.3, was stored at 5 °C in 3 ml glass vials and samples tested at 0.5, 1, 2, 3, and 4 months. Stability results are shown in Table 3. Turbidity, percent recovered protein and purity was determined as described above.

**Table 3. Stability of 40 mg/ml VEGF Trap Protein (VGFT-SS207)**

| Months | Visual Appearance | Turbidity | pH | % VEGF Trap Recovered | % VEGF Trap Native Configuration |
|---|---|---|---|---|---|
| 0 | Pass | 0.00 | 6.3 | 100 | 99.5 |
| 0.5 | Pass | 0.00 | 6.3 | 99 | 99.4 |
| 1 | Pass | 0.00 | 6.2 | 98 | 99.5 |
| 2 | Pass | 0.00 | 6.2 | 95 | 99.2 |
| 3 | Pass | 0.01 | 6.4 | | |
| 4 | Pass | 0.01 | 6.3 | | |

**Example 4. Stability of 40 mg/ml VEGF Trap Liquid Formulation Stored at 5°C in Pre-filled Glass Syringe.**

**[0059]** A liquid formulation containing 40 mg/ml VEGF trap (SEQ ID NO:4), 10 mM phosphate, 40 mM NaCl, 0.03% polysorbate 20, 5% sucrose, and pH 6.3, was stored at 5 °C in 1 ml prefilled luer glass syringe with 4023/50 FluroTec coated plunger and samples tested at 0.5, 1, 2, 3, and 4 months. Stability results are shown in Table 4. Turbidity, percent recovered protein and purity was determined as described above.

**Table 4. Stability of 40 mg/ml VEGF Trap Protein (VGFT-SS207)**

| Months | Visual Appearance | Turbidity | pH | % VEGF Trap Recovered | % VEGF Trap Native Configuration |
|---|---|---|---|---|---|
| 0 | Pass | 0.00 | 6.3 | 100 | 99.4 |
| 0.5 | Pass | 0.00 | 6.3 | 100 | 99.3 |
| 1 | Pass | 0.00 | 6.3 | 100 | 99.4 |
| 2 | Pass | 0.00 | 6.3 | 97 | 99.1 |
| 3 | Pass | 0.01 | 6.4 | | |
| 4 | Pass | 0.01 | 6.3 | | |

**Example 5. Stability of 40 mg/ml VEGF Trap Liquid Formulation Stored at 5°C in 3 ml Glass Vials.**

**[0060]** A liquid formulation containing 40 mg/ml VEGF trap (SEQ ID NO:4), 10 mM phosphate, 135 mM NaCl, 0.03% polysorbate 20, and pH 6.3, was stored at 5 °C in 3 ml glass vials and samples tested at 0.5, 1, 2, 3, and 4 months. Stability results are shown in Table 5. Turbidity, percent recovered protein and purity was determined as described above.

Table 5. Stability of 40 mg/ml VEGF Trap Protein (VGFT-SS203)

| Months | Visual Appearance | Turbidity | pH | % VEGF Trap Recovered | % VEGF Trap Native Configuration |
|---|---|---|---|---|---|
| 0 | Pass | 0.00 | 6.3 | 100 | 99.3 |
| 0.5 | Pass | 0.00 | 6.2 | 87 | 99.2 |
| 1 | Pass | 0.00 | 6.2 | 88 | 99.1 |
| 2 | Pass | 0.00 | 6.3 | 103 | 99.2 |
| 3 | Pass | 0.00 | 6.3 | 88 | 99.0 |
| 4 | Pass | 0.00 | 6.2 | 85 | 98.9 |
| 5 | Pass | 0.00 | 6.3 | 84 | 99.0 |

**Example 6. Stability of 40 mg/ml VEGF Trap Liquid Formulation Stored at 5°C in 1 ml Pre-filled Glass Syringe.**

**[0061]** A liquid formulation containing 40 mg/ml VEGF trap (SEQ ID NO:4), 10 mM phosphate, 135 mM NaCl, 0.03% polysorbate 20, and pH 6.3, was stored at 5 °C in 1 ml prefilled glass luer syringe with 4023/50 FluroTec coated plunger and samples tested at 0.5, 1, 2, 3, 4, and 5 months. Stability results are shown in Table 6. Turbidity, percent recovered protein and purity was determined as described above.

Table 6. Stability of 40 mg/ml VEGF Trap Protein (VGFT-SS203)

| Months | Visual Appearance | Turbidity | pH | % VEGF Trap Recovered | % VEGF Trap Native Configuration |
|---|---|---|---|---|---|
| 0 | Pass | 0.00 | 6.3 | 100 | 99.2 |
| 0.5 | Pass | 0.01 | 6.3 | 101 | 99.2 |
| 1 | Pass | 0.00 | 6.3 | 101 | 99.2 |
| 2 | Pass | 0.00 | 6.3 | - | - |
| 3 | Pass | 0.01 | 6.3 | 102 | 99.1 |
| 4 | Pass | 0.01 | 6.3 | 103 | 98.8 |
| 5 | Pass | 0.00 | 6.3 | 99 | 98.9 |

**Example 7. Stability of Lyophilized 20 mg/ml VEGF Trap Formulation Stored at 5°C in 3 ml Glass Vials and Reconstituted to 40 mg/ml.**

**[0062]** 0.8 ml of a liquid formulation containing 20 mg/ml VEGF trap (SEQ ID NO:4), 5 mM phosphate, 20 mM NaCl, 0.015% polysorbate 20, 2.5% sucrose, and pH 6.3, were lyophilized in 3 ml glass vials. Samples were stored at 5°C and tested at 1, and 2 months. VEGF trap was reconstituted to a final concentration of 40 mg/ml VEGF Trap (final volume of 0.4 ml). Stability

results are shown in Table 7 (t = time in months; * = visual appearance; ** = reconstitution time). Turbidity, percent recovered protein and purity was determined as described above.

**Table 7. Stability of Lyophilized 20 mg/ml VEGF Trap Protein (VGFT-SS216)**

| t | Vis. App.* | Recon. Time** (min) | Vis. App.* Reconst'd Liquid | Turbidity | pH | % VEGF Trap Recovered | % VEGF Trap Native Config. |
|---|---|---|---|---|---|---|---|
| 0 | Pass | 0.6 | Pass | 0.00 | 6.3 | 100 | 99.5 |
| 1 | Pass | 0.6 | Pass | 0.01 | 6.3 | 105 | 99.4 |
| 2 | Pass | 0.4 | Pass | 0.01 | 6.2 | 103 | 99.3 |

**Example 8. Stability of Lyophilized 20 mg/ml VEGF Trap Formulation Stored at 5°C in 3 ml Glass Vials.**

**[0063]** 0.8 ml of a liquid formulation containing 20 mg/ml VEGF trap (SEQ ID NO:4), 5 mM phosphate, 67.5 mM NaCl, 0.015% polysorbate 20, and pH 6.3, were lyophilized in 3 ml glass vials. Samples were stored at 5°C and tested at 1, 2, and 3 months. VEGF trap was reconstituted to a final concentration of 40 mg/ml VEGF trap (final volume of 0.4 ml). Stability results are shown in Table 8 (t = time in months; * = visual appearance; ** = reconstitution time).

**Table 8. Stability of Lyophilized 20 mg/ml VEGF Trap Protein (VGFT-SS216)**

| t | Vis. App.* | Recon. Time** (min) | Vis. App. Reconst'd Liquid | Turbidity | pH | % VEGF Trap Recovered | % VEGF Trap Native Config. |
|---|---|---|---|---|---|---|---|
| 0 | Pass | 0.7 | Pass | 0.00 | 6.3 | 100 | 99.0 |
| 1 | Pass | 0.7 | Pass | 0.01 | 6.2 | 105 | 98.9 |
| 2 | Pass | 0.4 | Pass | 0.01 | 6.2 | 103 | 98.9 |

**We claim:**

1. An ophthalmic formulation of a vascular endothelial growth factor (VEGF) antagonist, comprising

(a) 1-100 mg/ml a VEGF antagonist comprising the amino acid sequence of SEQ ID NO:4;

(b) 0.01-5% of one or more organic co-solvent(s) which is one or more of polysorbate, polyethylene glycol (PEG), and propylene glycol;

(c) 30-150 mM of a tonicity agent selected from sodium chloride or potassium chloride; and,

(d) 5-40 mM of sodium phosphate buffer; and optionally further comprising 1.0-7.5% of a stabilizing agent is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, or mannitol, pH between about 5.8-7.0.

2. An ophthalmic formulation according to claim 1, comprising about 1-100 mg/ml, preferably 10-80 mg/ml, of the VEGF antagonist, 10 mM sodium phosphate buffer, 40 mM NaCl, 0.03% polysorbate, and 5% sucrose, pH about 6.2-6.3.

3. An ophthalmic formulation according to claim 2, comprising VEGF antagonist at a concentration selected from the group consisting of 10 mg/ml, 20 mg/ml, 40 mg/ml, and 80 mg/ml.

4. An ophthalmic formulation according to any one of the above claims, comprising 10-80 mg/ml VEGF antagonist, 10 mM sodium phosphate, 0.03% polysorbate, and 135 mM sodium chloride, pH about 6.2-6.3.

5. A lyophilizable formulation of a vascular endothelial growth factor (VEGF) antagonist, comprising

(a) 5-50 mg/ml of the VEGF antagonist, preferably 5 mg/ml, 10 mg/ml, 20 mg/ml or 40 mg/ml comprising the amino acid sequence of SEQ ID NO:4;

(b) 5-25 mM of sodium phosphate buffer, pH about 5.8-7.0;

(c) 0.01-0.15% of an organic co-solvent, selected from the group consisting of polysorbate, polyethylene glycol (PEG), propylene glycol, and a combination thereof; and, optionally

(d) 1-10% of a stabilizing agent selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol; or 20-150 mM of a tonicity agent, preferably sodium chloride; or 1-10% of the stabilizing agent and 20-150 mM of the tonicity agent.

6. A lyophilizable formulation according to claim 5, comprising about 20 mg/ml of the VEGF

antagonist, about 10 mM sodium phosphate buffer, about 0.03% polysorbate, about 0.1% PEG, and about 2.5% sucrose, pH about 6.2-6.3.

7. A lyophilizable formulation according to claim 5, comprising about 20 mg/ml of the VEGF antagonist, about 5 mM sodium phosphate buffer, about 0.015% polysorbate, about 2.5% sucrose, and further comprising sodium chloride at about 20 mM, pH about 6.2-6.3.

8. A lyophilizable formulation according to claim 6, comprising about 20 mg/ml of the VEGF antagonist, about 5 mM sodium phosphate buffer, about 0.015% polysorbate, and further comprising sodium chloride at about 67.5 mM, pH about 6.2-6.3.

9. A method of producing a lyophilized formulation of a VEGF antagonist, comprising subjecting the pre-lyophilized formulation according to claim 5 to 8 to lyophilization to generate a lyophilized formulation.

10. A pre-filled syringe suitable for intravitreal administration comprising the formulation of claim 1.

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(54) **Title**: DEVICE AND METHOD FOR INTRAOCULAR DRUG DELIVERY

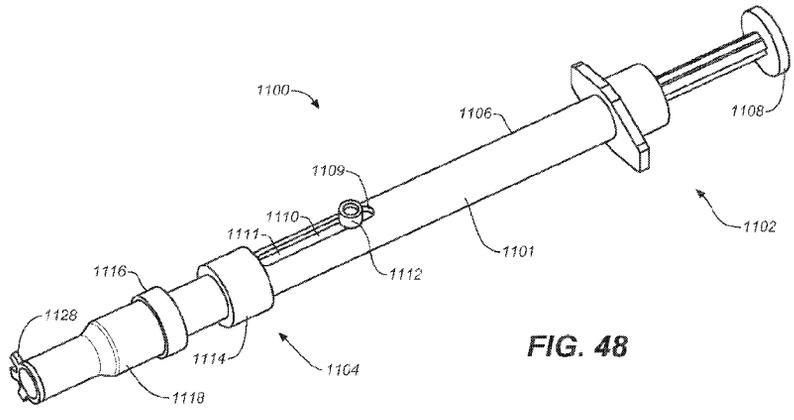


FIG. 48

(57) **Abstract**: Injection devices for delivering pharmaceutical formulations into the eye are described. The devices may be integrated to include features that allow safe and atraumatic manipulation of the devices with one hand. For example, accurate placement, including proper angulation, of the device on the eye and injection of a pharmaceutical formulation into the eye can be performed using one hand. The devices may also include improved safety features. For example, the devices may include an actuation mechanism that controls the rate and depth of injection into the eye. Some devices include a dynamic resistance component capable of adjusting the amount of pressure applied to the eye surface. Related methods and systems comprising the devices are also described.

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# DEVICE AND METHOD FOR INTRAOCULAR DRUG DELIVERY

## CROSS-REFERENCE TO RELATED APPLICATIONS

**[0001]** This application claims priority to U.S. Application No. 13/077,929, filed on March 31, 2011, which is hereby incorporated by reference in its entirety.

## FIELD

**[0002]** Described here are devices that are configured to safely and accurately deliver pharmaceutical formulations into the eye. Specifically, the devices may integrate various features that allow easy manipulation of the devices, and which may be beneficial for positioning of the devices on the ocular surface and for injecting pharmaceutical formulations atraumatically within the eye. Systems and methods for intraocularly delivering the pharmaceutical formulations using the devices are also described.

## BACKGROUND

**[0003]** The eye is a complex organ comprised of many parts that enable the process of sight. Vision quality depends on the condition of each individual part and the ability of these parts to work together. For example, vision may be affected by conditions that affect the lens (e.g., cataracts), retina (e.g., CMV retinitis), or the macula (e.g., macular degeneration). Topical and systemic drug formulations have been developed to treat these and other ocular conditions, but each has its drawbacks. For example, topical therapies that are applied on the surface of the eye typically possess short residence times due to tear flow that washes them out of the eye. Furthermore, delivery of drugs into the eye is limited due to the natural barrier presented by the cornea and sclera, and additional structures if the intended target resides within the posterior chamber. With respect to systemic treatments, high doses of drug are often required in order to obtain therapeutic levels within the eye, which increases the risk of adverse side-effects.

**[0004]** Alternatively, intravitreal injections have been performed to locally deliver pharmaceutical formulations into the eye. The use of intravitreal injections has become more common due to the increased availability of anti-vascular endothelial growth factor agents for the treatment of acute macular degeneration (AMD). Agents approved by the FDA for intravitreal injection to treat AMD include ranibizumab (Lucentis®: Genetech, South San

Francisco, CA) and pegaptanib sodium (Macugen®: Eyetech Pharmaceuticals, New York, NY). In addition, intravitreal bevacizumab (Avastin®: Genentech, South San Francisco, CA) has been widely used in an off-label application to treat choroidal neovascularization. Increased interest in developing new drugs for delivery directly into the vitreous for the treatment of macular edema, retinal vein occlusion, and vitreous hemorrhage also exists.

**[0005]** Currently, commercially available intravitreal injection devices lack many features that are useful in exposing the site of injection, stabilizing the device against the sclera, and/or controlling the angle and depth of injection. Many of the devices described in the patent literature, e.g., WO 2008/084064 and U.S. 2007/0005016, are also part of multi-component systems that are generally time consuming to set up and use. The increased procedure time associated with these devices may in turn increase the risk of complications. Further, having to manipulate many components by itself may increase the risk of complications due to user error. A serious complication of intraocular injection is intraocular infection, termed endophthalmitis that occurs due to the introduction of pathogenic organisms such as bacteria from the ocular surface into the intraocular environment, or trauma to the ocular surface tissues such as corneal or conjunctival abrasion.

**[0006]** Accordingly, new devices for performing intravitreal injections would be desirable. Ergonomic devices that simplify the injection procedure and reduce the risk of complications would be useful. Devices that accurately and atraumatically inject drugs, e.g., liquid, semisolid, or suspension-based drugs, into the eye would also be useful.

## SUMMARY

**[0007]** Described here are devices, methods, and systems for delivering pharmaceutical formulations into the eye. The devices may be integrated. By "integrated" it is meant that various features that may be beneficial in delivering the pharmaceutical formulations into the eye, e.g., in a safe, sterile, and accurate manner, are combined into a single device. For example, features that may aid appropriate placement on the desired eye surface site, help position the device so that the intraocular space is accessed at the proper angle, help to keep the device tip stable without moving or sliding on the ocular surface once it has been positioned during the entire drug injection, adjust or control intraocular pressure, and/or help to minimize trauma, e.g., from the force of drug injection or contact or penetration of the eye wall itself, may be integrated into a single device. More specifically, the integrated devices

may be used in minimizing trauma due to direct contact with the target tissue or indirectly through force transmission through another tissue or tissues such as the eye wall or vitreous gel, as well as minimizing trauma to the cornea, conjunctiva, episclera, sclera, and intraocular structures including, but not limited to, the retina, the choroid, the ciliary body, and the lens, as well as the blood vessels and nerves associated with these structures. Features that may be beneficial in reducing the risk of intraocular infectious inflammation such as endophthalmitis and those that may reduce pain may also be included. It should be understood that the pharmaceutical formulations may be delivered to any suitable target location within the eye, e.g., the anterior chamber or posterior chamber. Furthermore, the pharmaceutical formulations may include any suitable active agent and may take any suitable form. For example, the pharmaceutical formulations may be a solid, semi-solid, liquid, etc. The pharmaceutical formulations may also be adapted for any suitable type of release. For example, they may be adapted to release an active agent in an immediate release, controlled release, delayed release, sustained release, or bolus release fashion.

**[0008]** In general, the devices described here include a housing sized and shaped for manipulation with one hand. The housing typically has a proximal end and a distal end, and an ocular contact surface at the housing distal end. A conduit in its pre-deployed state will usually reside within the housing. The conduit will be at least partially within the housing in its deployed state. In some instances, the conduit is slidably attached to the housing. The conduit will generally have a proximal end, a distal end, and a lumen extending therethrough. An actuation mechanism may be contained within the housing that is operably connected to the conduit and a reservoir for holding an active agent. A trigger may also be coupled to the housing and configured to activate the actuation mechanism. In one variation, a trigger is located on the side of the device housing in proximity to the device tip at the ocular contact surface (the distance between the trigger and device tip ranging between 5 mm to 50 mm, between 10 mm to 25 mm, or between 15 mm to 20 mm), so that the trigger can be easily activated by a fingertip while the device is positioned over the desired ocular surface site with the fingers of the same hand. In another variation, a trigger is located on the side of the device housing at 90 degrees to a measuring component, so that when the device tip is placed on the eye surface perpendicular to the limbus, the trigger can be activated with the tip of the second or third finger of the same hand that positions the device on the ocular surface. In one variation, a measuring component is attached to the ocular contact surface. In some variations, a drug loading mechanism is also included.

**[0009]** The actuation mechanism may be manual, automated, or partially automated. In one variation, the actuation mechanism is a spring-loaded actuation mechanism. Here the mechanism may include either a single spring or two springs. In another variation, the actuation mechanism is a pneumatic actuation mechanism.

**[0010]** The application of pressure to the surface of the eye may be accomplished and further refined by including a dynamic resistance component to the injection device. The dynamic resistance component may include a slidable element coupled to the housing. In some variations, the slidable element comprises a dynamic sleeve configured to adjust the amount of pressure applied to the eye surface. In other variations, the dynamic resistance component is configured as an ocular wall tension control mechanism.

**[0011]** In one variation, the injection device includes a housing sized and shaped for manipulation with one hand, the housing having a proximal end and a distal end, a resistance band at least partially surrounding the housing having a thickness between about 0.01 mm to about 5 mm, a dynamic resistance component having proximal end and a distal end, an ocular contact surface at the housing or device distal end; a conduit at least partially within the housing, the conduit having a proximal end, a distal end, and a lumen extending therethrough, and an actuation mechanism coupled to the housing and operably connected to the conduit and a reservoir for holding an active agent.

**[0012]** In another variation, the injection device includes integrated components and includes a housing sized and shaped for manipulation with one hand, the housing having a proximal end and a distal end, and a sectoral measuring component coupled to a distal end of the housing or device. The sectoral measuring component may have a circumference or periphery, or have a central (core) member having a proximal end, a distal end, and a circumference, and comprising a plurality of radially extending members. The injection device may also include a conduit at least partially within the housing, the conduit having a proximal end, a distal end, and a lumen extending therethrough, an actuation mechanism coupled to the housing and operably connected to the conduit and a reservoir for holding an active agent, and a dynamic resistance component.

**[0013]** In yet a further variation, the injection device may include a housing sized and shaped for manipulation with one hand, the housing having a wall, a proximal end and a distal end, an ocular contact surface at the housing or device distal end, a conduit at least

partially within the housing, the conduit having a proximal end, a distal end, and a lumen extending therethrough, an actuation mechanism coupled to the housing and operably connected to a reservoir for holding an agent, a dynamic resistance component, and a filter coupled to the device.

**[0014]** In use, the devices deliver drug into the intraocular space by positioning an ocular contact surface of the integrated device on the surface of an eye, where the device further comprises a reservoir for holding an active agent and an actuation mechanism, and applying pressure against the surface of the eye at a target injection site using the ocular contact surface, and then delivering an active agent from the reservoir into the eye by activating the actuation mechanism. The steps of positioning, applying, and delivering are completed with one hand. In some instances, a topical anesthetic is applied to the surface of the eye before placement of the device on the eye. An antiseptic may also be applied to the surface of the eye before placement of the device on the eye.

**[0015]** The application of pressure against the surface of the eye using the ocular contact surface may also generate an intraocular pressure ranging between 15 mm Hg to 120 mm Hg, between 20 mm Hg to 90 mm Hg, or between 25 mm Hg to 60 mm Hg. As further described below, the generation of intraocular pressure before deployment of the dispensing member (conduit) may reduce scleral pliability, which in turn may facilitate the penetration of the conduit through the sclera, decrease unpleasant sensation associated with the conduit penetration through the eye wall during an injection procedure and/or prevent backlash of the device.

**[0016]** The drug delivery devices, components thereof, and/or various active agents may be provided in systems or kits as separately packaged components. The systems or kits may include one or more devices as well as one or more active agents. The devices may be preloaded or configured for manual drug loading. When a plurality of active agents is included, the same or different active agents may be used. The same or different doses of the active agent may be used as well. The systems or kits will generally include instructions for use. They may also include anesthetic agents and/or antiseptic agents.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0017]** FIGS. 1A-1B depict front views of exemplary ocular contact surfaces.

**[0018]** FIGS. 2A-2C show side views of additional exemplary ocular contact surfaces that include measuring components.

**[0019]** FIGS. 3A1-3A3 and FIGS. 3B1-3B3 show side views of other exemplary ocular contact surfaces.

**[0020]** FIGS. 4A and FIGS. 4B1-4B2 depict perspective and front views of an exemplary flanged ocular contact surface.

**[0021]** FIGS. 5A1-5A2 and FIGS. 5B1-5B2 depict side and perspective views of exemplary flat and convex ocular contact surfaces.

**[0022]** FIGS. 6A1-6A2 and FIGS. 6B1-6B2 show side and front views of exemplary soft or semi-solid ocular contact surfaces.

**[0023]** FIGS. 7A1-7A2, FIGS. 7B1-7B2, FIGS. 7C1-7C2, and FIGS. 7D-7E show additional exemplary ocular contact surfaces, including ocular contact surfaces having a high-traction interface.

**[0024]** FIG. 8 illustrates how an exemplary measuring component works to retract the eyelid and measure a certain distance from the limbus.

**[0025]** FIGS. 9A-9C show exemplary arrangements of measuring components around an ocular contact surface.

**[0026]** FIGS. 10A-10C depict other exemplary measuring components and how they work to measure a certain distance from the limbus.

**[0027]** FIGS. 11A-11D show further exemplary measuring components.

**[0028]** FIG. 12 shows an exemplary device that includes a marking tip member.

**[0029]** FIG. 13 illustrates how marks made on the surface of the eye by an exemplary marking tip member can be used to position the device at a target injection site.

**[0030]** FIGS. 14A-14C show perspective views of exemplary sharp conduits.

**[0031]** FIGS. 15A1-15A2 show side views of exemplary bevel angles.

**[0032]** FIGS. 16A-16D depict cross-sectional views of exemplary conduit geometries.

**[0033]** FIG. 17 depicts a cross-sectional view of additional exemplary conduit geometries.

**[0034]** FIGS. 18A-18C show side and cross-sectional views (taken along line A—A) of an exemplary flattened conduit.

**[0035]** FIG. 19 shows an exemplary mechanism for controlling exposure of the conduit.

**[0036]** FIG. 20 provides another exemplary conduit exposure control mechanism.

**[0037]** FIG. 21 shows an exemplary device having a front cover and back cover.

**[0038]** FIG. 22 illustrates how the device may be filled with a pharmaceutical formulation using an exemplary drug loading member.

**[0039]** FIGS. 23A-23C depict other examples of drug loading members.

**[0040]** FIGS. 24A-24D show an exemplary fenestrated drug loading member.

**[0041]** FIGS. 25A-25B show an exemplary fenestrated drug loading member interfaced with a drug source.

**[0042]** FIGS. 26A-26C depicts a side, cross-sectional view of an exemplary two-spring actuation mechanism.

**[0043]** FIG. 27 is a side, cross-sectional view of another exemplary two-spring actuation mechanism.

**[0044]** FIG. 28 depicts a perspective view of a device including a further example of a two-spring actuation mechanism in its pre-activated state.

**[0045]** FIG. 29 is a cross-sectional view of the device and two-spring actuation mechanism shown in FIG. 28.

**[0046]** FIG. 30 is a cross-sectional view of the device shown in FIG. 28 after the two-spring actuation mechanism has been activated.

**[0047]** FIGS. 31A-31C illustrate how the trigger in FIG. 28 actuates the first spring of the two-spring actuation mechanism to deploy the conduit.

**[0048]** FIGS. 32A-32C are expanded views that illustrate how release of the locking pins in FIG. 28 work to activate the second spring of the two-spring actuation mechanism.

**[0049]** FIGS. 33A-33B depict the device of FIG. 28 with an exemplary loading port.

**[0050]** FIG. 34 is a perspective view of an exemplary device with a pneumatic actuation mechanism.

**[0051]** FIGS. 35A-35B provide cross-sectional views of the device shown in FIG. 34. FIG. 35A show the pneumatic actuation mechanism in a pre-activated state. FIG. 35B shows the pneumatic actuation mechanism after deployment of the conduit.

**[0052]** FIG. 36 is a cross-sectional view of an exemplary device including a single spring actuation mechanism.

**[0053]** FIG. 37 is a cross-sectional view of the device shown in FIG. 36 that showing the single spring actuation mechanism after deployment of the conduit.

**[0054]** FIG. 38 is a side, cross-sectional view of an exemplary drug-loading piston.

**[0055]** FIGS. 39A-39I depict various views of exemplary device tips.

**[0056]** FIG. 40 shows an exemplary device with a sliding cap.

**[0057]** FIGS. 41A-41B provide cross-sectional views of another exemplary device having a two-spring actuation mechanism.

**[0058]** FIG. 42 depicts an enlarged sectional view an exemplary dynamic sleeve.

**[0059]** FIGS. 43A-43D illustrate an exemplary method of advancement of a dispensing member and drug injection.

**[0060]** FIGS. 44A-44D depict exemplary positional indicator components.

**[0061]** FIGS. 45A-45J show various aspects of exemplary fine sleeve mobility control components.

**[0062]** FIG. 46 is a graphic depiction of the amount of resistance force generated by a dynamic sleeve according to one variation.

**[0063]** FIG. 47 depicts an end view of an exemplary sectoral measuring component.

**[0064]** FIG. 48 shows a perspective view of one variation of an intraocular injection device.

**[0065]** FIGS. 49A and 49B are expanded views of the exemplary dynamic sleeve shown in FIG. 48. FIG. 49A depicts a side view of the sleeve. FIG. 49B is a cross-sectional view of the sleeve shown in FIG. 49A taken along line B-B.

**[0066]** FIG. 50 is an expanded end view of the sectoral measuring component shown in FIG. 48.

**[0067]** FIG. 51 depicts a sectoral measuring component according to another variation on the surface of the eye at the corneo-scleral limbus.

**[0068]** FIGS. 52A-52C show an exemplary access (drug loading) port in the injection device housing as well as an exemplary stopper for sealing an injection device access port, and how the location of the stopper corresponds with the location of an opening in a reservoir.

## DETAILED DESCRIPTION

**[0069]** Described here are hand-held devices, methods, and systems for delivering, e.g., by injection, pharmaceutical formulations into the eye. The devices may integrate (combine) various features that may be beneficial in delivering the pharmaceutical formulations into the eye, e.g., in a safe, sterile, and accurate manner, into a single device. Thus, features that may aid appropriate placement on the eye, help positioning so that the intraocular space is accessed at the proper angle, adjust or control intraocular pressure, and/or help to minimize trauma to the sclera and intraocular structures, e.g., from the force of injection or penetration of the sclera itself, may be integrated into a single device. The devices, in whole or in part, may be configured to be disposable.

### I. DEVICES

**[0070]** In general, the integrated devices described here include a housing sized and shaped for manipulation with one hand. The housing typically has a proximal end and a distal end, and an ocular contact surface at the housing distal end. A conduit tin its pre-deployed state may reside within the housing. The conduit will be at least partially within the housing in its

deployed state. In some variations, the conduit is slidably attached to the housing. Additionally, the conduit will generally have a proximal end, a distal end, and a lumen extending therethrough. An actuation mechanism may be contained within the housing that is operably connected to the conduit and a reservoir for holding an active agent.

**[0071]** The devices or portions thereof may be formed from any suitable biocompatible material or combination of biocompatible materials. For example, one or more biocompatible polymers may be used to make, e.g., the device housing, ocular contact surface, measuring component, etc. Exemplary biocompatible and non-biodegradable materials include without limitation, methylmethacrylate (MMA), polymethylmethacrylate (PMMA), polyethylmethacrylate (PEM), and other acrylic-based polymers; polyolefins such as polypropylene and polyethylene; vinyl acetates; polyvinylchlorides; polyurethanes; polyvinylpyrollidones; 2-pyrrolidones; polyacrylonitrile butadiene; polycarbonates; polyamides; fluoropolymers such as polytetrafluoroethylene (e.g., TEFLON™ polymer); polystyrenes; styrene acrylonitriles; cellulose acetate; acrylonitrile butadiene styrene; polymethylpentene; polysulfones; polyesters; polyimides; natural rubber; polyisobutylene rubber; polymethylstyrene; silicone; and copolymers and blends thereof.

**[0072]** In some variations, the device or a portion of the device such as the drug reservoir, plunger, housing, ocular contact surface, or measuring component, is made of a material that includes a cyclic olefin series resin. Exemplary cyclic olefin resins include without limitation, commercially available products such as Zeonex® cyclo olefin polymer (ZEON Corporation, Tokyo, Japan) or Crystal Zenith® olefinic polymer (Daikyo Seiko, Ltd., Tokyo, Japan) and APEL™ cyclo olefin copolymer (COC) (Mitsui Chemicals, Inc., Tokyo, Japan), a cyclic olefin ethylene copolymer, a polyethylene terephthalate series resin, a polystyrene resin, a polybutylene terephthalate resin, and combinations thereof. In one variation, it may be beneficial to use a cyclic olefin series resin and a cyclic olefin ethylene copolymer that have high transparency, high heat resistance, and minimal to no chemical interaction with a pharmacological product such as a protein, a protein fragment, a polypeptide, or a chimeric molecule including an antibody, a receptor or a binding protein.

**[0073]** The cyclic olefin polymers or the hydrogenation products thereof can be ring-opened homopolymers of cyclic olefin monomers, ring-opened copolymers of cyclic olefin monomers and other monomers, addition homopolymers of cyclic olefin monomers, addition copolymers of cyclic olefin monomers and other monomers, and hydrogenation products of

such homopolymers or copolymers. The above cyclic olefin monomers may include monocyclic olefin monomers, and polycyclic olefin monomers including bicyclic and higher cyclic compounds. Examples of the monocyclic olefin monomers suitable for the production of the homopolymers or copolymers of the cyclic olefin monomers are monocyclic olefin monomers such as cyclopentene, cyclopentadiene, cyclohexene, methylcyclohexene and cyclooctene; lower-alkyl derivatives thereof containing, as substituent groups, 1 to 3 lower alkyl groups such as methyl and/or ethyl groups; and acrylate derivatives thereof.

**[0074]** Examples of the polycyclic olefin monomers are dicyclopentadiene, 2,3-dihydrocyclopentadiene, bicyclo[2,2,1]-hepto-2-ene and derivatives thereof, tricyclo[4,3,0,$1^{2,5}$ ]-3-decene and derivatives thereof, tricyclo[4,4,0,$1^{2,5}$]-3-undecene and derivatives thereof, tetracyclo[4,4,0,$1^{2,5}$,$0^{7,10}$]-3-dodecene and derivatives thereof, pentacyclo[6,5,1,$1^{3,6}$,$0^{2,7}$,$0^{9,13}$ 4-pentadecene and derivatives thereof, pentacyclo[7,4,0,$1^{2,5,0}$,$0^{8,13}$,$1^{9,12}$]-3-pentadecene and derivatives thereof, and hexacyclo[6,6,1,$1^{3,6}$,$1^{10,13}$,$0^{2,7}$,$0^{9,14}$]-4-heptadecene and derivatives thereof. Examples of bicyclo[2,2,1]-hepto-2-ene derivatives include 5-methyl-bicyclo[2,2,1]-hepto-2-ene, 5-methoxy-bicyclo[2,2,1]-hepto-2-ene, 5-ethylidene-bicyclo[2,2,1]-hepto-2-ene, 5-phenyl-bicyclo[2,2,1]-hepto-2-ene, and 6-methoxycarbonyl-bicyclo[2,2,1-]-hepto-2-ene. Examples of tricyclo[4,3,0,$1^{2,5}$]-3-decene derivatives include 2-methyl-tricyclo[4,3,0,$1^{2,5}$]-3-decene and 5-methyl-tricyclo[4,3,0,$1^{2,5}$]-3-decene. Examples of tetracyclo[4,4,0,$1^{2,5}$]-3-undecene derivatives include 10-methyl-tetracyclo[4,4,0,$1^{2,5}$]-3-undecene, and examples of tricyclo[4,3,0,$1^{2,5}$]-3-decene derivatives include 5-methyl-tricyclo[4,3,0,$1^{2,5}$]-3-decene.

**[0075]** Examples of tetracyclo[4,4,0,$1^{2,5}$,$0^{7,10}$]-3-dodecene derivatives include 8-ethylidene-tetracyclo-[4,4,0,$1^{2,5}$,$0^{7,10}$]-3-dodecene, 8-methyl-tetracyclo-[4,4,0,$1^{2,5}$,$0^{7,10}$]-3-dodecene, 9-methyl-8-methoxy-carbonyl-tetracyclo[4,4,0,$1^{2,5}$,$0^{7,10}$]-3-dodecene, 5,10-dimethyl-tetracyclo[4,4,0,$1^{2,5}$,$0^{7,10}$]-3-dodecene. Examples of hexacyclo[6,6,1,$1^{3,6}$,$1^{10,13}$,$0^{2,7}$, $0^{9,14}$]-4-heptadecene derivatives include 12-methyl-hexacyclo[6,6,1,$1^{3,6}$,$1^{10,13}$,$0^{2,7}$,$0^{9,14}$]-4-heptadecene and 1,6-dimethyl-hexacyclo[6,6,1,$1^{3,6}$,$1^{10,13}$,$0^{2,7}$, $0^{9,14}$]-4-heptadecene. One example of the cyclic olefin polymer is an addition homopolymer of at least one cyclic olefin monomer or an addition copolymer of at least one cyclic olefin monomer and at least one other olefin monomer (for example, ethylene, propylene, 4-methylpentene-1, cyclopentene, cyclooctene, butadiene, isoprene, styrene, or the like). This homopolymer or copolymer can be obtained by polymerizing the above monomer or monomers, for example, while using as a

catalyst a known catalyst which is soluble in a hydrocarbon solvent and is composed of a vanadium compound or the like and an organoaluminum compound or the like (Japanese Patent Application Laid-Open (Kokai) No. HEI 6-157672, Japanese Patent Application Laid-Open (Kokai) No. HEI 5-43663).

**[0076]** Another example of the cyclic olefin polymer is a ring-opened homopolymer of the above monomer or a ring-opened copolymer of the above monomers. It can be obtained by homopolymerizing the above monomer or copolymerizing the above monomers, for example, while using as a catalyst a known catalyst such as (1) a catalyst composed of a halide or the nitrate of a platinum group metal such as ruthenium, rhodium, palladium, osmium or platinum and a reducing agent or (2) a catalyst composed of a compound of a transition metal such as titanium, molybdenum or tungsten and an organometal compound of a metal in one of Groups I to IV of the periodic table such as an organoaluminum compound or organotin compound (Japanese Patent Application Laid-Open (Kokai) No. HEI 6-157672, Japanese Patent Application Laid-Open (Kokai) No. HEI 5-43663).

**[0077]** The homopolymer or copolymer may contain unsaturated bonds. The homopolymer or copolymer may be hydrogenated using a known hydrogenation catalyst. Examples of the hydrogenation catalyst include (1) Ziegler-type homogeneous catalysts which are each composed of an organic acid salt of titanium, cobalt, nickel or the like and an organometal compound of lithium, aluminum or the like, (2) supported catalysts which are each composed of a carrier such as carbon or alumina and a platinum metal such as palladium or ruthenium supported on the carrier, and (3) catalysts which are each composed of a complex of one of the above-described platinum group metal (Japanese Patent Application Laid-Open (Kokai) No. HEI 6-157672).

**[0078]** In some variations, the device or a portion of the device such as the drug reservoir is made of a material that comprises a rubber. Examples of suitable rubber materials include butyl rubbers such as butyl rubber, chlorinated butyl rubber, brominated butyl rubber, and divinylbenzene-copolymerized butyl rubber; conjugated diene rubbers such as polyisoprene rubber (high to low cis-1,4 bond), polybutadiene rubber (high to low cis-1,4 bond), and styrene-butadiene copolymer rubber; and ethylene-propylene-diene terpolymer rubber (EPDM). Crosslinkable rubber materials may also be used, and may be made by kneading the above-described rubber materials together with additives such as a crosslinking agent, a filler and/or reinforcement, a colorant, or an age resister.

**[0079]** In some variations, the biocompatible material is a biodegradable polymer. Non-limiting examples of suitable biodegradable polymers include cellulose and ester, polyacrylates (L-tyrosine-derived or free acid), poly(β-hydroxyesters), polyamides, poly(amino acid), polyalkanotes, polyalkylene alkylates, polyalkylene oxylates, polyalkylene succinates, polyanhydrides, polyanhydride esters, polyaspartimic acid, polylactic acid, polybutylene digloclate, poly(caprolactone), poly(caprolactone)/poly(ethylene glycol) copolymers, polycarbone, L-tyrosin-derived polycarbonates, polycyanoacrylates, polydihydropyrans, poly(dioxanone), poly-p-dioxanone, poly(ε-caprolactone-dimethyltrimethylene carbonate), poly(esteramide), polyesters, aliphatic polyesters, poly(etherester), polyethylene glycol/poly(orthoester) copolymers, poly(glutarunic acid), poly(glycolic acid), poly(glycolide), poly(glycolide)/poly(ethylene glycol) copolymers, poly(lactide), poly(lactide-co-caprolactone), poly(DL-lactide-co-glycolide), poly(lactide-co-glycolide)/poly(ethylene glycol) copolymers, poly(lactide)poly(ethylene glycol) copolymers, polyphosphazenes, polyphosphesters, polyphophoester urethanes, poly(propylene fumarate-co-ethylene glycol), poly(trimethylene carbone), polytyrosine carbonate, polyurethane, terpolymer (copolymers of glycolide lactide or dimethyltrimethylene carbonate), and combinations, mixtures or copolymers thereof.

**[0080]** Additives may be added to polymers and polymer blends to adjust their properties as desired. For example, a biocompatible plasticizer may be added to a polymer formulation used in at least a portion of a device to increase its flexibility and/or mechanical strength, or to provide color contrast with respect to the surface of the eye. In other instances, a biocompatible filler such as a particulate filler, fiber and/or mesh may be added to impart mechanical strength and or rigidity to a portion of a device.

**[0081]** The devices described here can be manufactured, at least in part, by injection or compression molding the above-described materials.

**[0082]** In some instances, it may be beneficial to include a removably attached or integrated viewing and/or magnifying element on the device. For example, a magnifying glass and/or illumination source such as a LED light may be removably attached to the device to facilitate the visualization of the tip of the device and the injection site. The improved visualization may help to more precisely and safely position the device at a target location, e.g., about 3.5 mm to 4 mm posterior to the corneo-scleral limbus, so that complications of intraocular injection such as retinal detachment, ciliary body bleeding, or trauma to the

intraocular lens can be potentially avoided. The magnifying glass may be made from any suitable material, e.g., it may be made from any suitable non-resorbable (biodegradable) material previously described, but will typically be light-weight so that it does not affect the balance of the injection device. The magnifying glass and/or illumination source, e.g., the LED, may be disposable.

Housing

**[0083]** The housing of the device generally contains the drug reservoir and actuation mechanism. In its first, non-deployed state (pre-deployed state), the conduit may reside within the housing. The housing may be of any suitable shape, so long as it allows grasping and manipulation of the housing with one hand. For example, the housing may be tubular or cylindrical, rectangular, square, circular, or ovoid in shape. In some variations, the housing is tubular or cylindrical, similar to the barrel of a syringe. In this instance, the housing has a length between about 1 cm and about 15 cm, between about 2.5 cm and about 10 cm, or about 4 cm and about 7.5 cm. For example, the housing may have a length of about 1 cm, about 2 cm, about 3 cm, about 4 cm, about 5 cm, about 6 cm, about 7 cm, about 8 cm, about 9 cm, about 10 cm, about 11 cm, about 12 cm, about 13 cm, about 14 cm, or about 15 cm. The surface of the housing may also be texturized, roughened, or otherwise modified in certain areas, e.g., with protrusions, ridges, etc., to aid the grip and or manipulation of the housing by the user. Grips may be associated with any one of the actuation mechanisms further described below. The grips are generally configured to help the operator maintain a steady grip on the device using, e.g., two, three or four fingers. The plunger actuation lever may be located on the device housing in the close proximity of the grip, for example, integrated with the grip, or between about 1.0 mm and 10 mm of the grip, so that the operator is able to easily use the fingers holding the device to actuate, e.g., slide, the actuation lever while maintaining a steady grip and without compromising the hold/control of the device. The distance that the actuation lever may travel may be between about 2.0 mm and about 8.0 mm, or between about 1.0 mm and about 15 mm). Maintaining a steady grip while actuating the drug injection mechanism is useful because it helps to localize the injection site on the eye surface with about a 0.5 mm precision accuracy

**[0084]** The housing may be made from any suitable material. For example, and as previously stated, the components of the device may be made from any suitable biocompatible material or combination of biocompatible materials. Materials that may be

beneficial in making the housing include, without limitation, a cyclic olefin series resin, a cyclic olefin ethylene copolymer, a polyethylene terephthalate series resin, a polystyrene resin, and a polyethylene terephthalate resin. In one variation, it may be beneficial to use a cyclic olefin series resin and a cyclic olefin ethylene copolymer that have a high transparency, a high heat resistance, and minimal to no chemical interaction with a pharmacological product such as a protein, a protein fragment, a polypeptide, or a chimeric molecule including an antibody, a receptor or a binding protein. Additional materials that may be beneficial in making the housing include, without limitation, fluoropolymers; thermoplastics such as polyetheretherketone, polyethylene, polyethylene terephthalate, polyurethane, nylon, and the like; and silicone. In some variations, the housing may be made from a transparent material to aid confirmation of conduit deployment and/or drug delivery. Materials with suitable transparency are typically polymers such as acrylic copolymers, acrylonitrile butadiene styrene (ABS), polycarbonate, polystyrene, polyvinyl chloride (PVC), polyethylene terephthalate glycol (PETG), and styrene acrylonitrile (SAN). Acrylic copolymers that may be useful include, but are not limited to, polymethyl methacrylate (PMMA) copolymer and styrene methyl methacrylate (SMMA) copolymer (e.g., Zylar 631® acrylic copolymer).

Ocular Contact Surfaces

**[0085]** The devices described herein generally include an atraumatic ocular contact surface at the distal end of the housing. In some variations, the ocular contact surface is fixedly attached to the housing proximal end. In other variations, the ocular contact surface is removably attached to the housing proximal end. The ocular contact surface will typically be sterile. In some instances, the ocular contact surface is disposable. In use, the ocular contact surface of the device is placed on the surface of the eye.

**[0086]** The ocular contact surface may be of any suitable configuration, e.g., size, shape, geometry, etc., as long as it allows atraumatic placement of the device on the ocular surface. In some variations, the ocular contact surface is ring-shaped (e.g., FIGS. 1A-1B). When the ocular contact surface takes the shape of a ring, it may have a diameter of about 0.3 mm to about 8 mm, about 1 mm to about 6 mm, or about 2 mm to about 4 mm. In other variations, the ocular contact surface is oval or circular in shape.

**[0087]** More specifically, as shown in the front views of FIGS. 1A-1B, the device tip comprises a ring-shaped ocular contact surface where the distance between the inner diameter and outer diameter of the ring forms a rim. In this instance, the ring-shaped ocular contact surface may be configured as having a wider ocular contact surface (10) (rim) and smaller internal opening (12) (FIG. 1A), or narrower ocular contact surface (14) (rim) with larger internal opening (16) (FIG. 1B). The dispensing member (conduit) may be an injection needle that is hidden inside and protected by the device tip. A membrane may also be provided that extends across the internal opening, and which may be flush with the ocular contact surface or recessed within the lumen of the device tip where the injection needle resides.

**[0088]** As shown in FIGS. 39A-39B, the tip of the dispensing member may be recessed relative to end of the device housing tip comprising the ocular contact surface in the resting state, so that when the device tip is placed in contact with any surface such as the skin or the eye wall, the tip of the dispensing member is separated from the surface by a distance marked with arrows in FIG. 39B. This distance may ensure that the dispensing member tip does not come in direct contact with any surface prior to the injection procedure, which prevents accidental bacterial contamination of the dispensing member from sources such as skin secretions, ocular secretions or tears, and minimizes the risk of introducing intraocular infectious agents during the intraocular injection procedure that may cause endophthalmitis.

**[0089]** In some variations, the tip of the dispensing member is recessed relative to, and is separated from the closest end of the device housing by a distance ranging from about 0.01 mm to about 10 mm, from about 0.1 mm to about 5 mm, or from about 0.5 mm to about 2 mm.

**[0090]** An enclosure may be provided on the distal end of the device that completely covers the dispensing member to prevent it from contacting eye lashes or eye lids, and to prevent it from being exposed to potentially contaminated surfaces at all times. Here the dispensing member may extend from the enclosure and penetrate the eye wall and into an eye cavity without being exposed to ocular appendages such as eyelids or eye lashes that harbor bacteria. The eye is an immune-privileged organ and, thus, any bacterial contamination has the propensity to result in intraocular infection. Enclosure of the dispensing member may protect it from contacting ocular appendages harboring bacteria, thereby minimizing the risk of sight-threatening intraocular infection. In one variation, the dynamic sleeve (further

described below) is configured as the sterile enclosure. The dynamic sleeve may also be covered by a membrane that prevents ocular surface tears from entering the orifice of the device tip and potentially contaminating the dispensing member before it is deployed.

**[0091]** In other variations, the outer surface of the device tip may be configured to include a raised surface that forms a seal around the exit site of the dispensing member from the device tip. The seal may function to prevent ocular tears from circulating through the potential injection site once the device tip has been positioned on the eye surface. The raised surface may be configured to be annular, oval, square, rectangular, triangular or any other suitable shape or geometry.

**[0092]** In another variation, the ocular contact surface of the device tip that comes in direct contact with the eye surface is ring-shaped, where there is a clearing between the internal wall of the device housing and the dispensing member of about 360 degrees, which is marked by arrows in FIG. 39C. Here, if the ring-shaped ocular interface surface becomes contaminated with an infectious agent and is placed onto the eye surface, the dispensing member will come in contact and penetrate through the eye surface that is separated from the contaminated device tip by the area of clearing, which prevents accidental bacterial contamination of the dispensing member and minimizes the risk of introducing intraocular infection that may cause endophthalmitis. In contrast, the lack of such clearing around the dispensing member, as shown in FIG. 39D, may allow accidental infectious contamination of the device tip at the site of injection.

**[0093]** In some variations, there is a clearing between the internal wall of the device housing and the dispensing member ranging from about 0.1 mm to about 5 mm, from about 0.3 mm to 3 mm, or from about 0.5 mm to about 2 mm.

**[0094]** In other variations, there is a solid membrane or partition (105) that separates the tip of the dispensing member (107) from the external environment, as shown in FIG. 39E, where the membrane or partition may be water-impermeable and/or be air-impermeable. The membrane or partition may ensure that there is no air movement in or out of the device creating an air seal and maintaining a certain constant air pressure inside the device.

**[0095]** Furthermore, the membrane or partition may ensure that the dispensing member tip does not come in contact with any source of accidental bacterial contamination such as tears and ocular secretions prior to the injection procedure, which prevents accidental bacterial

contamination of the dispensing member and minimizes the risk of introducing intraocular infection during the intraocular injection procedure that may cause endophthalmitis.

**[0096]** The membrane or partition that separates the tip of the dispensing member from the end of the device housing may comprise a material selected from the group consisting of biocompatible and non-biodegradable materials including without limitation, methylmethacrylate (MMA), polymethylmethacrylate (PMMA), polyethylmethacrylate (PEM), and other acrylic-based polymers; polyolefins such as polypropylene and polyethylene; vinyl acetates; polyvinylchlorides; polyurethanes; polyvinylpyrollidones; 2-pyrrolidones; polyacrylonitrile butadiene; polycarbonates; polyamides; fluoropolymers such as polytetrafluoroethylene (e.g., TEFLON$^{TM}$ polymer); or fluorinated ethylene propylene (FEP); polystyrenes; styrene acrylonitriles; cellulose acetate; acrylonitrile butadiene styrene; polymethylpentene; polysulfones; polyesters; polyimides; natural rubber; polyisobutylene rubber; polymethylstyrene; silicone; derivatives and copolymers and blends thereof.

**[0097]** In some variations, the membrane or partition (30) may be recessed inside the device tip so that when the device tip is placed in contact with any surface such as the skin or the eye surface, the said membrane or partition is separated from the said surface by a distance marked with arrows, as depicted in FIG. 39E. The distance may ensure that the dispensing member tip (31) does not come in direct contact with any surface prior to the injection procedure, which prevents accidental bacterial contamination of the dispensing member from sources such as skin secretions, ocular secretions or tears, and minimizes the risk of introducing intraocular infection during the intraocular injection procedure that may cause endophthalmitis.

**[0098]** The membrane or partition may be recessed relative to and separated from the end of the device housing at the ocular interface by a distance ranging from about 0.01 mm to about 10 mm, from about 0.1 mm to about 5 mm, or from about 0.5 mm to about 2 mm.

**[0099]** In further variations, a measuring component (32) (further described below) may be recessed relative to the end of the device housing (33) at the ocular contact surface (FIGS. 39F-39H), so that when the device tip (34) comes in contact with the eye surface (35) (FIG. 39I), the measuring component (32) does not come in contact with the eye surface (35). This configuration may minimize the risk of trauma to the delicate tissue covering the eye surface such as the non-keratinizing epithelia of the cornea and conjunctiva. Avoiding direct contact

between the measuring member and the ocular surface may be beneficial in minimizing the risk of ocular surface trauma such as corneal or conjunctival abrasion, which prevents further serious complications such as bacterial injection including corneal ulcer. In alternative variations, the tip of the measuring member (32) may be angled away or towards the eye (FIGS. 39G and 39H, respectively). The measuring component may be recessed relative to the end of the device housing by a distance ranging from about 0.01 mm to about 5 mm, from about 0.1 mm to about 3 mm, or from about 0.5 mm to about 2 mm.

**[0100]** In some variations, as shown in FIGS. 2A-2C, the device tip may also comprise a ring-shaped ocular contact surface and a measuring means that helps to determine the proper location of the injection site at a certain distance relative to and perpendicular to the corneo-scleral limbus. In one variation, the measuring component (20) is located on one side of the device tip (22). In another variation, more than one measuring component is located on more than one side of the device tip. Here the tip of the measuring component is flat (FIG. 2C) and does not substantially protrude above the ocular contact surface. In other variations, the tip of the measuring component is raised (FIGS. 2A-2B) above the ocular contact surface, which enables it to prevent the eyelid from sliding over and on top of the measuring component, thus preventing the eyelid from coming into contact with the sterile ocular contact surface of the device tip or the dispensing member. This in turn may reduce the risk of accidental contamination and intraocular infection during the injection procedure.

**[0101]** In other variations, the ocular contact surface comprises a flange (e.g., FIGS. 3A1-3A3, FIGS. 3B1-3B3, FIG. 4A, and FIGS. 4B1-4B2). The flange may provide an expanded contact surface between the device tip and the eye surface, thus increasing the stability of the device when it is positioned on the ocular surface, and decreasing the pressure force per unit area of the device-ocular interface. Reducing the pressure force per unit area of the device-ocular interface in turn may reduce the potential for conjunctival damage by the device tip when it is pressed against the eye wall. Avoiding such conjunctival damage is desirable because the conjunctiva is covered by delicate non-keratinizing epithelium containing multiple sensory nerve endings and pain receptors.

**[0102]** In some variations, the flange may have thin edges that come in contact with the ocular surface, and which allows the eye lid to travel over and on top of the flange, but prevents the eye lid from coming in contact with the sterile ocular contact surface of the device tip. The ocular contact surface may also be a ring-shaped flange (e.g., FIGS. 4A and

4B1-4B2). Such a ring-shaped flange may also prevent the eye lid from coming in contact with the sterile ocular contact surface of the device tip.

**[0103]** More specifically, as shown in FIG. 3, the flange may have a thin edge (FIG. 3A1), which allows the eye lid to slide over the said flange and come in contact with the shaft of the device tip. In an alternative variation, the said flange may be thick (FIG. 3B1) in order to prevent the eye lid from sliding over it and keeping it from coming in contact with the device shaft, thus preventing inadvertent contamination of the injection site. When the flange at the ocular contact surface of the device tip is thick, its edges, such as those at its ocular surface may be rounded in order to prevent accidental damage to the ocular surface tissues such as the conjunctiva that is covered with delicate non-keratinizing epithelium rich in nerve endings and pain receptors. In alternative variations of the device tip, the ocular contact interface may be flat (FIGS. 3A1 and 3B1), convex (FIGS. 3A2 and 3B2), or concave (FIGS. 3A3 and 3B3) to reduce the chance of accidental damage to ocular surface tissues such as the conjunctiva while providing a means of applying a force onto the eye wall and increasing intraocular pressure in order to facilitate the needle penetration through the eye wall, as well as to partially immobilize the eye during the injection procedure by providing the traction interface of the ocular contact surface. FIGS. 4A and 4B1-4B2 illustrate perspective and front views of a flanged ocular contact surface.

**[0104]** In yet further variations, the ocular contact surface may be configured to be flat, convex, concave, or slanted (e.g., FIGS. 5 and 7). In FIGS. 5A1-5A2, the device tip has a flat ocular contact surface. In an alternative variation, the device tip has a protruding or convex ocular contact surface (FIGS. 5B1-5B2), which may improve contact between the internal opening of the device tip and the ocular surface when the device tip is pressed against the eye wall resulting in eye wall indentation. In yet another variation, the ocular contact surface of the device tip is indented or concave, which reduces the risk of accidental damage to the ocular surface tissue such as the conjunctiva. Such configurations of the ocular contact surface of the device tip may reduce the chance of accidental damage to ocular surface tissues, such as the conjunctiva, while providing a means of applying a pressure force onto the eye wall and increasing the intraocular pressure in order to facilitate the needle penetration through the eye wall, as well as to partially immobilize the eye during the injection procedure by providing the device-ocular surface traction interface.

**[0105]** More specifically, as shown in FIG. 7, the ocular contact surface may be flat and perpendicular to the long axis of the said device (FIGS. 7A1-7A2), or is flat and slanted relative to the long axis of the said device (7B1-7B2) (e.g., oriented at an angle other than 90 degrees, such as from about 45 degrees to about 89 degrees relative to the long axis of the device), or is convex and perpendicular to the long axis of the device (FIG. 7C1), or is convex and slanted relative to the long axis of the device (FIG. 7C2), or is rounded (FIG. 7D), or is oval (FIG. 7E). In one variation, the ocular interface is rounded or oval (e.g., similar to the tip of a Q-tip). The thickness of the ocular contact surface may be from about 0.01 mm to about 10 mm, from about 0.05 mm to about 5 mm, or from about 0.1 mm to about 2 mm.

**[0106]** The ocular contact surface may include one or more features that help to stabilize it on the eye surface. For example, in one variation, the ocular contact surface comprises a plurality of traction elements, e.g., bumps, ridges, raised details above the plane of the ocular contact surface, etc., that increase surface traction of the ocular contact surface on the eye surface without being abrasive. Such an ocular contact surface may provide a medium- or high-traction interface to stabilize the device on the surface of the eye and prevent it from moving during intraocular drug delivery. In another variation, the ocular contact surface includes an adherent interface such as a suction mechanism. Varying the type of material used to make the ocular contact surface may also help prevent its slippage on the ocular surface.

**[0107]** The materials used to make the ocular contact surface may also help to prevent abrasion, scratching, or irritation of the eye surface. Exemplary non-abrasive materials that may be employed include without limitation, nylon fiber, cotton fiber, hydrogels, spongiform materials, styrofoam materials, other foam-like materials, silicone, plastics, PMMA, polypropylene, polyethylene, fluorinated ethylene propylene (FEP), and polytetrafluoroethylene (PTFE). These materials may be smooth-hard, semi-hard, or soft, and may be beneficial in preventing conjunctival abrasion, subconjunctival hemorrhage during transcleral needle deployment, or other accidental trauma to the ocular surface tissues (FIG. 6). Materials typically used in contact lens manufacturing may also be employed.

**[0108]** In some variations, the edges of the ocular contact surface are also rounded to prevent accidental damage to the ocular surface tissues such as the conjunctiva that is covered with delicate non-keratinizing epithelium rich in nerve endings and pain receptors. In this

instance, as shown in FIG. 6, the ocular contact surface may have a circumference corresponding to the circumference of the device tip (FIGS. 6A1-6A2). In other variations, the circumference of the ocular contact surface may protrude beyond the circumference of the shaft of the device tip, thus forming a flange (FIGS. 6B1-6B2). The flange may increase the ocular contact surface of the device tip while maintaining the slim profile of the shaft of the tip, enabling its easy insertion into the interpalprebral fissure of the eye.

**[0109]** The ocular contact surface may also provide an interface surface that is pliable or deformable, and which conforms to the surface of the eye when placed against the said eye surface during the intraocular drug delivery procedure. The surface of the eye that comes in direct contact with the said interface surface of the disclosed device includes, but is not limited to, the surface of the eye over the pars plana region defined as the circumferential area between about 2 mm and 7 mm posterior to and surrounding the limbus, or the corneo-scleral limbal area between about 2 mm anterior and about 2 mm poster to and circumferential to the limbus. The interface surface that conforms to the curvature of the surface of the eye may enable the formation of an optimal contact interface between the device and the eye, and may ensure sterility of the intraocular drug delivery process and immobilization of the eye, which in turn may enhance the safety of the injection procedure. Examples of ocular interface materials for the device are those that are generally able to conform to the surface of the eye (that is deformable or pliable) particularly to the curvature of the external surface of the eye in the area of pars plana about 2-5 mm posterior to the corneo-scleral limbus for intravitreal drug application, as well as to the area of the corneo-scleral limbus for anterior chamber drug applications. As previously stated, materials that are non-abrasive to the non-keratinizing conjunctival and corneal epithelium of the ocular surface may be used. Specifically, the materials and their configurations (e.g., foam, braid, knit, weave, fiber bundle, etc.), may include those capable of forming medium- or high-traction surfaces (e.g., hydrogels or cotton) that enable immobilization of the eye globe during the injection procedure.

**[0110]** In some variations, the material of the ocular contact surface changes its properties upon contact with fluid, e.g., by reducing its traction coefficient such as in cotton fiber, which may reduce the risk of conjunctival abrasion upon contact of the ocular contact surface with the eye surface. In other variations, the material comprising ocular contact surface does not

change its physical and chemical properties when exposed to fluid that covers the surface of the eye such as tears.

**[0111]** The ocular contact surfaces described here may be beneficial in preventing conjunctival and/or episcleral bleeding during intraocular needle injection. For example, a device comprising a ring-shaped ocular interface may be pressed against the eye wall, which in turn applies pressure to the conjunctival and episcleral vessels, thereby reducing blood flow therethrough. Given the reduced blood flow through these vessels, the risk of subconjunctival bleeding during intraocular injection procedure may be reduced. Following the completion of intraocular drug application, the needle is withdrawn, but the ring-shaped tip may remain pressed against the eye wall, thus applying continuous pressure onto the conjunctival and episcleral vessels and further reducing the risk of bleeding and/or minimizing the extent of bleeding.

**[0112]** In some variations, the device comprises an ocular contact surface that functions as a drug reservoir. Here a drug may be incorporated into, or coated on, the material of the ocular contact surface. The drug may then diffuse, leech, etc., from the ocular contact surface onto the surface of the eye. Exemplary materials for inclusion of drugs are hydrogels and their derivatives.

**[0113]** The ocular contact surface may also cover the dispensing member (conduit) such as an injection needle (e.g., it may be a cap that entirely covers the needle), which may enable the injector to apply pressure onto the eye by pressing the tip (e.g., the distal end of the cap) against the eye wall. This in turn may increase the intraocular pressure before the needle comes in contact with the eye wall and, thus, may facilitate needle penetration because the eye wall is more taut in comparison to an eye wall being penetrated by a needle on a conventional syringe. Needle penetration is typically more difficult with a conventional syringe because the lower intraocular pressure that is generated makes the eye wall more deformable and mobile. In addition, the device tip that covers the dispensing member (conduit), such as an injection needle, may also protect the said dispensing member from being contaminated by its accidental contact with eye lids.

Intraocular Pressure Control Mechanisms (Ocular Wall Tension Control Mechanisms)

**[0114]** The control of intraocular pressure (IOP) during the drug delivery procedure, e.g., intraocular injection or intravitreal injection, may be beneficial. The application of limited intraocular pressure before deployment of the dispensing member (conduit) may reduce scleral pliability, which in turn may decrease any unpleasant sensation on the eye surface during an injection procedure and/or prevent backlash of the device. The term "backlash" typically refers to the inability of the conduit to smoothly penetrate the eye wall due to scleral pliability and elasticity, which makes the sclera indent to a certain point and push the conduit and device backwards before the conduit penetrates into and through the sclera. Accordingly, the devices described here may include one or more IOP control mechanisms, also referred to herein as ocular wall tension control mechanisms. This is because ocular wall tension is proportionally related to, and determined in part, by intraocular pressure. Other factors that may effect wall tension are scleral thickness and rigidity, which can be variable due to patient age, gender, and individual variations.

**[0115]** The IOP mechanisms may control IOP during the placement and positioning of the device tip at the target location on the ocular surface, and/or intraocular or intravitreal positioning of the dispensing member (conduit) during intraocular or intravitreal injection of a drug. For example, the IOP mechanisms may control IOP prior to and during the intraocular or intravitreal positioning of a dispensing member being used for trans-scleral or trans-corneal penetration. Once penetration of the ocular surface by the dispensing member occurs, IOP will typically decrease. This decrease in IOP may occur immediately after penetration of the ocular surface by the dispensing member.

**[0116]** In some variations, the IOP control mechanisms allow (enable) the devices to generate an IOP between 15 and 120 mm Hg during the placement and positioning of the device tip at a target location on the ocular surface, and/or intraocular positioning of the dispensing member. In other variations, the IOP control mechanisms allow (enable) the devices to generate an IOP between 20 and 90 mm Hg during the placement and positioning of the device tip at a target location on the ocular surface, and/or intraocular positioning of the dispensing member. In yet further variations, the IOP control mechanisms allow (enable) the devices to generate an IOP between 25 and 60 mm Hg during the placement and positioning of the device tip at a target location on the ocular surface, and/or intraocular positioning of the dispensing member.

**[0117]** The IOP control mechanisms may also allow (enable) the devices to maintain the IOP between 10 and 120 mm Hg, or between 15 and 90 mm Hg, or between 20 and 60 mmHg during any duration of time of the intraocular injection procedure. In some variations, the drug injection rate is slowed or completely aborted by the device if the intraocular pressure exceeds a certain predetermined value, for example 120 mm Hg, or 60 mm Hg, or 40 mm Hg. Here the IOP control mechanism may be configured to detect a IOP level during the intraocular drug injection of, e.g., 90 mmHg, or 60 mm Hg, or 40 mm Hg.

**[0118]** The IOP control mechanism may include a spring, or it may comprise a mechanical or an electrical control mechanism. In general, the IOP control mechanism will be configured to balance the frictional forces of the injection plunger and fluid injection resistance pressure (force required to push fluid through the needle into the pressurized eye fluids). The IOP control mechanisms may be coupled to the device housing and actuation mechanism in a manner that allows automatic adjustment of the force of dispensing member deployment and plunger advancement. That is, the IOP control mechanism may be configured to effect a predetermined level of force of the dispensing member and a predetermined intraocular pressure level. Again, use of the IOP control mechanisms may generate higher than the resting IOP prior to dispensing member deployment so that scleral elasticity and the potential for device backlash is decreased, and to facilitate scleral penetration by the dispensing member.

**[0119]** In one variation, the IOP control mechanism is a pressure relief valve that bypasses the injection stream once a maximum pressure is reached. In another variation, the IOP mechanism is a pressure accumulator that dampens the IOP within a specified range. Some variations of the IOP control mechanism may include a pressure sensor. In yet another variation, the IOP control mechanism includes a slidable cap that covers the dispensing member prior to its deployment, but which may slide or retract along the surface of the device housing to expose, deploy, or advance the dispensing member e.g., upon attainment of a predetermined IOP level. Sliding of the cap may be manually adjustable, e.g., using a dial, or automatically adjustable, step-wise, or incremental in nature. For example, as shown in FIG. 40, integrated injection device (500) includes, among other elements, a cap (502), a stop (504), a trigger (506), a spring (508), a plunger (510), a seal (512), a drug reservoir (514), a needle (516), and a syringe (518). In use, when cap (502) is placed against the ocular surface and pressure applied against the ocular surface, cap (502) slidably retracts proximally (in the

direction of the arrow) to stop (504) as the syringe (518) and needle (516) are advanced. The trigger (506), e.g., a lever, may then be depressed to release spring (508), which advances plunger (510) and seal (512) to inject drug from the drug reservoir (514) through needle (516). Once the drug is injected, cap (502) slides back over the needle (516).

**[0120]** A locking mechanism may also be used to prevent sliding of the cap, cover or ocular contact surface, or prevent deployment of the dispensing member until a predetermined IOP is reached. The locking mechanism may also be used to prevent sliding of the cap, cover, or ocular contact surface if a predetermined IOP is not reached. For instance, the locking mechanisms included on the devices described here that include a slidable cover, cap, etc., may be released manually or automatically when the IOP reaches a predetermined level, such as between 20 mm Hg and 80 mm Hg. Such locking mechanisms may include without limitation, high traction surfaces, locking pins, interlocking raised ridges, or any other type of locking mechanism that prevents the tip of the device, e.g., the cap or cover of the device, from sliding and thus exposing the needle.

**[0121]** In yet further variations, the IOP control mechanism includes a high-traction surface or raised ridges on the cap, cover, or ocular contact surface situated over the dispensing member. Such features may be disposed on the inner surface of the cap, cover, or ocular contact surface and configured so that upon sliding in the proximal direction, the high-traction surface or raised ridges mate with corresponding structures (e.g., crimps, dimples, protrusions, other raised ridges) on the surface of the device housing or other appropriate device component to provide resistance of the cap, cover, or ocular contact surface against the eye wall (thus increasing ocular wall tension and IOP). In this instance, the IOP control mechanism comprises a dynamic resistance component, as further described below. As stated above, the cap, cover, or ocular contact surface may be configured so that sliding is manually or automatically adjustable, step-wise, or incremental in nature. When raised ridges are employed, any suitable number may be used, and they may be of any suitable size, shape, and geometry. For example, the raised ridges may be circumferentially disposed within the cap, cover, or ocular contact surface. In some instances, the raised ridges are configured with surfaces of differing slope. For example, the distal surface may be configured to be steeper than the proximal surface. With this design, incremental sliding and incremental increases in IOP may be generated when the cap, cover, or ocular contact surface is slid proximally, but sliding of the cap, cover, or ocular contact surface back over the

dispensing member may also be accomplished due to the decreased slope of the proximal ridge surface.

Dynamic Resistance Component

**[0122]** The application of pressure to the surface of the eye may be accomplished and further refined by including a dynamic resistance component to the injection device. The dynamic resistance component may be configured to detach from the injection device. The dynamic resistance component may include a slidable element and/or a fully rotatable (e.g., rotate 360 degrees) or partially rotatable (e.g., rotate less than 360 degrees) element coupled to the housing. The dynamic resistance component may be configured so that it can be fully or partially rotated about the long axis of the device using only one finger (e.g., the middle finger) while holding the device with the thumb and the index finger of the same hand. In some variations, the slidable element comprises a dynamic sleeve configured to adjust the amount of pressure applied to the eye surface, as further described below. As previously stated, certain variations of the ocular wall tension control mechanism function as dynamic resistance components.

**[0123]** The dynamic resistance component may also be configured as a dynamic sleeve. Similar to the slidable cap previously described, the dynamic sleeve may be configured to increase intraocular pressure and tension of the eye wall prior to needle injection. However, the dynamic sleeve is capable of being manually manipulated to thereby adjust the amount of pressure applied on surface of the eye (and thus, the amount of eye wall tension). Having the ability to manually adjust the applied pressure may allow the injector (user) to have improved control of the injection site placement and the injection angle, and also enhances the user's ability to stably position the device on the ocular surface prior to needle deployment. In general, the dynamic sleeve is designed to enable the user to precisely position the device tip at the targeted site on the eye surface and to firmly press the device tip against the eye wall to increase wall tension and intraocular pressure. The dynamic sleeve may be used to raise intraocular pressure to a predetermined level, as described above, prior to the initiation of sleeve movement and needle deployment. It should be understood that the terms "dynamic sleeve," "sleeve," "dynamic sleeve resistance control mechanism," and "sleeve resistance mechanism" are used interchangeably throughout. The dynamic sleeve will generally be configured such that when the user exerts a pulling force (e.g., retraction) on the sleeve, this movement may facilitate needle exposure and reduce the amount of pressure force (down to 0

Newton) ("N" refers to the unit of force "Newton") needed to be applied to the eye wall in order to slide the sleeve back and expose the needle. The dynamic sleeve may also be configured such that when the user exerts a pushing force (e.g., advancement) on the sleeve, this movement may counteract and impede needle exposure, which may allow the device tip to apply increased pressure to the eye wall prior to the initiation of sleeve movement and needle exposure.

**[0124]** Some variations of the dynamic sleeve provide a variable force that follows a U-shaped curve, as described further in Example 1 and FIG. 46. Here the highest resistance is encountered at the beginning and the end of dynamic sleeve movement along the housing with decreased resistance between the start and end points of dynamic sleeve travel. In use, this translates to having an initial high-resistance phase (upon initial placement on the eye wall) followed by a decrease in resistance to sleeve movement during needle advancement into the eye cavity. When the needle is fully deployed, the dynamic sleeve will typically be at the end of its travel path, and increased resistance would again be encountered. This increase in resistive force allows the sleeve to come to a smooth, gradual stop (instead of an abrupt hard stop at the end point) to minimize the risk of transmitting damaging amounts of force to the inert eye wall (which in turn minimizes the risk of causing discomfort or injury to the eye). Here an exemplary dynamic sleeve may be configured to be tapered at the proximal end and distal end. Referring to the sectional view in FIG. 42, integrated injection device (42) includes a housing (44), a resistance band (46) wholly or partially surrounding the housing, and a dynamic sleeve (48) that can be slidably advanced and retracted upon the housing (44). When partially surrounding the housing, the resistance band may be referred to as a resistance strip. The dynamic sleeve (48) has a proximal end (50) and a distal end (not shown) that are tapered. The tapered ends may provide higher traction at the beginning and the end of the dynamic sleeve travel path along the device housing (44) (that is at the beginning and end of needle deployment). The taper at the proximal end (50) provides higher traction and resistance at the beginning of dynamic sleeve movement when it contacts resistance band (46). The thickness of the resistance band (46) may be varied to adjust the amount of resistance desired. For example, the thickness of the resistance band may range from about 0.01 mm to about 5 mm, or range from about 0.1 mm to about 1 mm. Specifically, the thickness of the resistance band may be about 0.05 mm, about 0.1 mm, about 0.2 mm, about 0.3 mm, about 0.4 mm, about 0.5 mm, about 0.6 mm, about 0.7 mm, about 0.75 mm, about 0.8 mm, about 0.9 mm, about 1.0 mm, about 1.5 mm, about 2.0 mm, about

2.5 mm, about 3.0 mm, about 3.5 mm, about 4.0 mm, about 4.5 mm, or about 5.0 mm. The width of the resistance band may also vary and be about 1.0 mm, about 1.5 mm, about 2.0 mm, about 2.5 mm, about 3.0 mm, about 3.5 mm, about 4.0 mm, about 4.5 mm, or about 5.0 mm. Upon reaching the wider middle segment (52), lower-traction and lower resistance movement is encountered, followed by higher traction and higher resistance at the end of needle deployment as the taper at the distal end of the dynamic sleeve is reached. As the dynamic sleeve becomes progressively more tapered at the distal end, more traction is produced against the device housing until it gradually comes to a complete stop. Instead of both ends being tapered, in some variations one of the proximal end and distal end of the dynamic sleeve may be tapered.

**[0125]** Variable traction force may also be provided by components such as circular raised bands or ridges on the outside surface of the device tip. These components may provide counter-traction when approximated against another circular raised band or ridge on the inside surface of the movable dynamic sleeve (inner bands or ridges). When the outer and inner bands or ridges are in contact with each other before the dynamic sleeve begins to move, they generate high traction and high resistance to dynamic sleeve movement. Once the dynamic sleeve starts to move, the raised band on the outside of the device housing moves past the raised band on the inside of the dynamic sleeve, which may result in a rapid decrease in resistance to dynamic sleeve movement and, therefore, decreased pressure on the eye wall by the device tip. The shape of the raised interlocking bands or ridges will generally determine the shape of resistance decrease. For example, the resistance decrease may follow a sine-shaped profile.

**[0126]** In another variation, the dynamic sleeve may generate a force that continuously decreases from its highest point before needle deployment (when the dynamic sleeve completely covers the needle), to its lowest point when the dynamic sleeve begins to move to expose the needle tip. Here the force remains low until the end of dynamic sleeve travel and complete needle deployment. This pattern of resistance decrease may follow a sine-shaped curve.

**[0127]** Slidable advancement of the dynamic sleeve may generate a force between itself and the housing ranging from 0 N to about 2 N. In some instances, slidable advancement of the dynamic sleeve generates a force between itself and the housing ranging from about 0.1 N to about 1 N.

Measuring Components

**[0128]** The devices described here may include a measuring component that may be useful in determining the location of the intraocular injection site on the eye surface. Integrated devices will generally include a measuring component. Some variations of the device may include a ocular contact surface having a high-traction surface integrated with a measuring component. The measuring component may be fixedly attached or removably attached to the ocular contact surface. The measuring component may also be configured to fully (360 degrees) or partially rotate (less then 360 degrees) about the long axis of the device housing. Inclusion of a rotatable (dynamic) measuring component may allow the operator to maintain a comfortable grasp of the device without having to change or reposition the finger placement pattern in order to appropriately orient the measuring component toward the limbus in any meridian either in the left or right eye of a mammal (for example perpendicular to the limbus), in order to accurately determine the injection site and before stably positioning the device tip on the eye surface. A rotating (dynamic) measuring component may also enable sterile localization of injection site in any meridian/clock hour relative to limbus circumference, while avoiding contact with the eyelids or eyelashes.

**[0129]** As previously stated, the measuring component may be raised above the ocular surface so that it prevents the eye lid from coming in contact with the sterile ocular contact surface of the device tip (e.g., FIGS. 2A-2B and 8). The specific configuration of the measuring component may also help to minimize the risk of inadvertent contamination of the sterile drug dispensing member (conduit) such as an injection needle. Such contamination may result from various causes such as the sterile needle coming in inadvertent contact with an eyelid or other non-sterile surface. The measuring components may also be colored in a manner to provide color contrast against the surface of the eye including the conjunctiva, the sclera, and the iris. The distance from the deployed needle tip to the tip of each individual measuring component may be about 4 mm. Here the distance from the needle tip to the outer edge of corneo-scleral limbus may be about 3.5 mm. In some instances, e.g., when the measuring component comprises two tabs, and the tabs are rotated so that the tips of the tabs are simultaneously touching the outer endge of corneo-scleral limbus, the injection site is located at 3.5 mm from limbus (ranging from 1 to 4 mm).

**[0130]** In general, the measuring component will enable the intraocular injection site to be more precisely placed at a specific distance from, and posterior or anterior to, the corneal-

scleral junction termed "the limbus." In some variations, the measuring component may provide for placement of the intraocular injection site from about 1 mm to about 5 mm, from about 2 mm to about 4.5 mm, or from about 3 mm to about 4 mm, from and posterior to the limbus. In another variation, the measuring component may provide for placement of the intraocular injection site from about 2 mm to about 5 mm posterior to the limbus, or about 3.5 mm posterior to the limbus. In other variations, the measuring component may provide for placement of the intraocular injection site from within about 3 mm or about 2 mm, from and anterior to, the limbus, or between about 0.1 mm and about 2 mm from and anterior to the limbus. In one variation, the measuring component provides for placement of the intraocular injection site between about 1 mm anterior to the limbus and about 6 mm posterior to the limbus. In another variation, the measuring component provides for placement of the intraocular injection site between about 3 mm to about 4 mm posterior to the limbus.

**[0131]** The measuring components may have any suitable configuration. For example, the measuring components may be located on one side of the ocular contact surface or on more than one side of the ocular contact surface (e.g., FIGS. 9, 10, and 11). Here, when the tip of the measuring component is placed right next to the corneo-scleral limbus, the site of the intraocular needle injection is placed at a particular distance from the limbus, e.g., between about 3 mm and about 4 mm posterior to the limbus.

**[0132]** In alternative variations, the measuring component comprises one or more members (e.g., FIGS. 9, 10, and 11). These members may radially extend from the ocular contact surface. Having more than one member comprise the measuring component may be beneficial in ensuring that the distance between the limbus and injection site is measured perpendicular to the limbus and not tangentially as it may be the case when the measuring means comprise a single member. When the tips of one or more than one radial member comprising the measuring component are aligned along the corneo-scleral limbus, the site of the intraocular needle injection is placed at a particular distance from the limbus, such as between about 3 mm and about 4 mm posterior to the limbus.

**[0133]** More specifically, as shown in FIG. 8, the device tip having an ocular contact surface comprises a measuring component (80) that enables the determination of the injection site at a certain distance relative to the corneo-scleral limbus. As previously stated, in one variation the measuring component is located on one side of the device tip. In another variation, more than one measuring component is located on more than one side of the device

tip. In yet further variations, the tip of the measuring component may be raised, bent, etc., which prevents the eye lid from sliding over the measuring component and coming in accidental contact with the dispensing member (conduit) of device. Also in FIG. 8, the dispensing member (conduit) is shown as being completely shielded inside the device tip.

**[0134]** FIG. 9 provides further detail about another variation of the measuring component. Here the device tip comprises a ring-shaped ocular contact surface (90) and a measuring component (91) that enables the determination of the injection site at a certain distance relative to the corneo-scleral limbus. The outer circumference of the device tip that comes into contact with the surface of the eye has, e.g., a ring shaped ocular interface, and the dispensing member such as an injection needle may be hidden inside and protected by the device tip. In FIG. 9, the measuring components (91) are located on one side of the device tip (FIGS. 9A-9B) or on more than one side of the device tip (FIG. 9C). Thus, when the tip of the measuring component is placed next to the corneo-scleral limbus, the site of intraocular needle injection is placed at a specific distance from the limbus, such as between about 3 mm and about 4 mm posterior to the limbus. Any suitable number of measuring components may be provided on the device tip, e.g., attached to the ocular contact surface. When a plurality of measuring components are used, they may be arranged around the ocular contact surface in any suitable fashion. For example, they may be circumferentially disposed around the ocular contact surface or on one side of the ocular contact surface. They may be equally or unequally spaced around the circumference of the ocular surface. In other variations, the measuring components may be symmetrically spaced or asymmetrically spaced around the circumference of the ocular contact surface. These configurations may be beneficial in allowing the injector to rotate the device along its long axis.

**[0135]** FIGS. 10A-10C provide additional views of measuring components that are similar to those shown in FIGS. 9A-9C. In FIG. 10, a ring-shaped ocular contact surface (93) is shown having a measuring component (93) that enables the determination of the injection site at a certain distance relative to and perpendicular to the corneo-scleral limbus (94). The measuring components are depicted on one side of the device tip, or in another variation, on more than one side of the device tip. Again, the measuring components may comprise one or more members. Having more than one member comprise the measuring component may be beneficial in ensuring that the distance between the limbus and injection site is measured perpendicular to the limbus and not tangentially as it may be the case when the measuring

component comprise a single member. When the tips of all members comprising the measuring component are aligned along the corneo-scleral limbus, the site of the intraocular needle injection is placed at a particular distance from the limbus, such as between about 3 mm and about 4 mm posterior to the limbus.

**[0136]** More than one measuring component is also shown in FIGS. 11A-11D. Here the measuring components (95) are depicted as extending from a common attachment point (96) on the ocular contact surface. When the tips of all members comprising the said measuring component are aligned along the corneo-scleral limbus, the site of the intraocular needle injection is placed at a particular distance from the limbus, such as between about 3 mm and about 4 mm posterior to the limbus.

**[0137]** Alternatively, the measuring components may be configured as one or more flexible measuring strips. Flexible materials that may be used to make the measuring strips include flexible polymers such as silicones. As shown in FIG. 44A, the measuring strip (800) may extend from the device tip (802), usually from the side of the ocular contact surface (804), so that the distance between the limbus and injection site can be measured perpendicular to the limbus. A positional indicator component (806) may be employed to ensure that the measuring strip (800) is properly used. For example, as shown in FIG. 44B, correct positioning of the measuring strip (800) (so that a 90 degree angle is formed between the measuring strip and device housing (808)) may be determined when the positional indicator component is substantially taut. In contrast, a slack positional indicator component (as shown in FIG. 44C) would indicate incorrect positioning. The positional indicator component may be a cord. In one variation, the integrated device comprises at least three measuring strips. In another variation, the integrated device includes at least four measuring strips. When a plurality of measuring strips are used, they may be configured in any suitable manner around the tip of the integrated device (equally spaced around the circumference of the ocular contact surface, symmetric or asymmetrically placed around the circumference of the ocular contact surface, etc.). For example, as shown in FIG. 44D, the measuring strips may be configured to span the desired 90 degree angle (45 degrees plus 45 degrees between the farthest strips) to allow for a 90 degree rotation of a control lever without having to reposition the hand of the user.

**[0138]** In some variations, the measuring component may be configured as a marking tip member (97). As shown in FIG. 12, the marking tip member (97) at its distal end (closer to

the eye) that interfaces with the ocular surface and leaves a visible mark (98) on the conjunctival surface when pressed against it (e.g., FIG. 13). The marker-tip enables intraocular injections to be carried out through a safe area of the eye relative to the corneo-scleral limbus (99), such as between about 3 mm and about 4 mm posterior to the limbus, over the pars plana region of the ciliary body of the eye. The diameter of the marking tip may range from about 1 mm to about 8 mm, or from about 2 mm to about 5 mm, or from about 2.3 mm to about 2.4 mm (e.g., FIG. 12).

**[0139]** In further variations, the measuring component may be a sectoral measuring component. The sectoral measuring component may be configured to span a sector of between about 1 degree and about 180 degrees of arc (e.g., between about 45 degrees and 90 degrees of arc) at the distal end of device or housing. In general, by "sectoral" it is meant that only a portion or section of the measuring component includes elements for taking measurements. For example, a sectoral measuring component may include radially extending members that are spaced from about 1 degree to about 90 degrees about the circumference of the device tip. During precise localization of the injection site, a sectoral measuring component configured in this manner may enhance sterility of the procedure because the measuring component can be oriented toward the limbus and away from periocular appendages such as the eyelids and eye lashes. Here the sectoral measuring component may avoid contact with the appendages, thus minimizing the risk of bacterial contamination and intraocular infection, while enabling precise localization of the injection site relative to the limbus in a sterile manner.

**[0140]** In one variation, the sectoral measuring component may comprise a central (core) member having a proximal end and a distal end, and comprising a plurality of radially oriented spokes or tabs as the radially extending members, which are equal in length. Central member may be round, oval, square, rectangular or triangular in shape having a circumference or a perimeter. When central member is round, its diameter may be between about 1.0 mm and about 8.0 mm, or between about 3.0 mm and about 6.0 mm. Radially extending members may have the same fixed angle between any two adjacent members, for example, between 1 degree and 90 degrees, or between 15 degrees and 45 degrees. The radially extending members may also have the same length, so that the distance between the needle exit point and the tip of each individual radial member tip is substantially the same, for example between about 1.0 mm and about 5.0 mm, or between about 3.0 mm and about

4.0 mm. With this configuration, the sectoral measuring component may provide fine adjustment of device positioning on the ocular surface around the limbus circumference while rotating the entire device between 1 and 180 degrees (or between 1 and 90 degrees) and using any one or plurality of spokes or tabs to measure the distance between injection site and the limbus. As shown in FIG. 47, using any single tab or spoke (1002), or any two adjacent tabs or spokes (1002) of a sectoral measuring component (1000) that simultaneously touch the limbus line enables the measurement of two fixed distances relative to the limbus, for example 4 mm and 3.5 mm, respectively. More specifically, when the measuring component is rotated so that the tip of only one tab or spoke touches the limbus line while the tab or spoke is perpendicular to the limbus line, the injection site is localized at about 4 mm (ranging from about 3 mm to about 5 mm) from the limbus. When the measuring component is rotated so that the tips of two tabs or spokes are simultaneously touching the limbus line, the injection site is at about 3.5 mm from limbus (ranging from about 1 mm to about 4 mm).

**[0141]** In another variation, three divergent measuring tabs or spokes may comprise the measuring component. In a further variation, two divergent measuring tabs or spokes may comprise the measuring component. The divergent measuring tabs or spokes may span a curvilinear distance between about 30 degrees and about 180 degrees or between about 45 degrees and about 90 degrees on the distal surface of the device tip. Having the measuring tabs or spokes protrude only on one side of the device tip that is oriented towards the limbus and away from the eyelid may be helpful in ensuring that the measuring tabs do not become contaminated by touching the eyelids or eyelashes.

Conduits

**[0142]** The intraocular drug delivery devices described here may include any suitable conduit (or dispensing member) for accessing the intraocular space and delivering active agents therein. The conduits may have any suitable configuration, but will generally have a proximal end, a distal end, and a lumen extending therethrough. In their first, non-deployed (pre-deployed) state, the conduits will generally reside within the housing. In their second, deployed state, i.e., after activation of the actuation mechanism, the conduit, or a portion thereof, will typically extend from the housing. By "proximal end" it is meant the end closest to the user's hand, and opposite the end near the eye, when the devices are positioned against the eye surface.

**[0143]** The distal end of the conduit will generally be configured to be sharp, beveled, or otherwise capable of penetrating the eye surface, e.g., the sclera. The conduit employed may be of any suitable gauge, for example, about 25 gauge, about 26 gauge, about 27 gauge, about 28 gauge, about 29 gauge, about 30 gauge, about 31 gauge, about 32 gauge, about 33 gauge, about 34 gauge, about 35 gauge, about 36 gauge, about 37 gauge, about 38 gauge, or about 39 gauge. The wall of the conduit may also have any suitable wall thickness. For example, in addition to regular wall (RW) thickness, the wall thickness of the conduit may be designated as thin wall (TW), extra/ultra thin wall (XTW/UTW), or extra-extra thin wall (XXTW). These designations are well known to those of skill in the relevant art. For example, the conduit may be a fine gauge cannula or needle. In some variations, the conduits may have a gauge between about 25 to about 39. In other variations, the conduits may have a gauge between about 27 to about 35. In yet further variations, the conduits may have a gauge between about 30 to about 33.

**[0144]** The conduits may have a sharp, pointed tip (FIGS. 14B-14C and FIGS. 15A1-15A2), rather than a rounded one (FIG. 14A) as in conventional needles. The pointed needle tip is formed by the lateral side surfaces that are straight at the point of their convergence into the tip, and at the point of their convergence forming a bevel angle (the angle formed by the bevel and the shaft of the needle), which may range from between about 5 degrees and about 45 degrees (FIG. 14B), between about 5 degrees and about 30 degrees, between about 13 degrees to about 20 degrees, or between about 10 degrees and about 23 degrees (FIG. 14C).

**[0145]** The sharp, pointed needle tip may provide improved penetration of the needle through the fibrillar, fibrous scleral tissue, which is the major structural cover of the eye and consists of a network of strong collagen fibers. Thus, such a needle tip during its penetration through the eye wall may create less resistance and, thus, decrease the impact force that is transmitted to the intraocular structures, such as the retina and the crystalline lens, in turn causing less damage to intraocular structures during the intraocular injection process (compared to conventional needles).

**[0146]** In addition, such a narrow bevel angle may enable the needle to cause less sensation when it penetrates through the eye wall (the outer cover of the said eye wall being richly innervated with sensory nerve fibers endings particularly densely located in the conjunctiva and cornea), which may be an issue when intraocular injections are involved compared to other less sensitive sites.

**[0147]** The narrow bevel angle may also allow for a longer bevel length and larger bevel opening and, thus, a larger opening at the distal end of the injection needle. With such a configuration, the force of drug injection into an eye cavity may be reduced, thus reducing the chances of intraocular tissue damage by a forceful stream of injected substance, which may occur with conventional short-beveled needles.

**[0148]** In some variations, the conduits are injection needles having one or more flat surface planes, as well as one or more side-cutting surfaces, as illustrated in FIGS. 16 and 17. Examples include a needle shaft comprising multiple surface planes separated by sharp ridges (FIGS. 16A-16C), as well as a needle tip comprising sharp side-cutting surfaces located on either side of the beveled surface of the needle about 90 degrees from the beveled surface (FIG. 17). The conduit may also be bi-beveled, i.e., have two bevels facing about 180 degrees from each other that is located on the opposite sides of the conduit. The conduit may also be coated (e.g., with silicone, PTFE, etc.) to facilitate its penetration through the eye wall.

**[0149]** In other variations, the conduit may be configured to be wholly or partially flattened in at least one dimension, as shown in the cross-sectional view of FIG. 18C taken along the line A—A of FIG. 18A. For example, the conduit may be flattened in the anterior-posterior dimension (that is from the beveled side of the needle towards its opposite side. In one variation, both the external and internal surfaces of the needle are flattened and represent ovals on cross-section. In another variation, the internal surface of the needle is round and represents a circle on cross-section, while the external surface of the needle is flattened to enable its easier penetration through the fibrous scleral or corneal tissue of the eye wall. In another variation, more than one external surface plane of the needle is flattened to enable its easier penetration through the fibrous eye wall, while the internal opening of the said needle may be of any shape including round or oval.

**[0150]** As previously stated, in its second, deployed state, the conduit or needle extends from the housing. The portion of the needle that extends from the housing can be referred to as the exposed needle length. Upon activation of the actuation mechanism, the needle goes from its first, non-deployed state (pre-deployed state) (where it is entirely within the housing of the device), to its second, deployed configuration outside the housing, where a certain length of it is exposed. This exposed length may range from about 1 mm to about 25 mm, from about 2 mm to about 15 mm, or from about 3.5 mm to about 10 mm. These exposed

needle lengths may enable complete intraocular penetration through the sclera, choroid and ciliary body into the vitreous cavity, while minimizing the risk of intraocular damage. In some variations, the exposed needle length ranges from about 1 mm to about 5 mm, or from about 1 mm to about 4 mm, or from about 1 mm to about 3 mm. Here the exposed needle lengths may enable complete intraocular penetration through the cornea into the anterior chamber, while minimizing the risk of intraocular damage.

**[0151]** In some variations, the devices may include an exposure control mechanism (9) for the dispensing member (11) (conduit) (FIGS. 19 and 20). The exposure control mechanism (9) generally enables one to set the maximal length of the dispensing member exposure during dispensing member deployment. In one variation, the exposure control mechanism works by providing a back-stop for the needle-protective member (13). In another variation, the exposure control mechanism (9) may be a rotating ring member with a dialable gauge. Needle exposure could be adjusted by the millimeter or a fraction of the millimeter, e.g., 1 mm, 1.5 mm, 2 mm, 2.5 mm, 3 mm, etc. Here the device may be equipped with a retraction mechanism that controls needle retraction into a needle-protective member. Such a needle-retraction mechanism may be spring-actuated (FIG. 20).

**[0152]** The devices may also include a removable distal (towards the eye) member that covers and protects the conduit (e.g., the front cover (15) in Figure 21). In one variation, the devices may also include a removable proximal (away the eye) member that covers and protects the proximal part of the device, e.g., comprising a loading dock mechanism (17) (e.g., the back cover (19) in Figure 21).

**[0153]** Some variations of the devices described herein comprise a needle stabilization mechanism configured to provide a steady and consistent needle alignment that is perpendicular to the ocular contact surface, and, therefore, perpendicular to the eye surface. This allows the operator to precisely control the angle of needle penetration into the eye by controlling the position of the device tip and housing relative to the eye surface. For example, the needle stabilization mechanism may be configured so that the needle exits the device tip through its central point (e.g., at the geometric center of a round tip) at 90 degrees relative to the tip outer surface (e.g., the ocular contact surface). In some instances, an injection angle other than 90 degrees (when the long axis of the device is not completely perpendicular to the eye surface at the injection site), may lead to inadvertent intraocular trauma to the crystalline lens or the retina. However, in other instances it may be useful for

the needle to exit the tip at an angle less than 90 degrees relative to eye surface, in a direction parallel to the limbus.

Reservoirs

**[0154]** The reservoir is generally contained within the housing and may be configured in any suitable manner, so long as it is capable of delivering an active agent to the intraocular space using the actuation mechanisms described herein. The reservoir may hold any suitable drug or formulation, or combination of drugs or formulations to the intraocular space, e.g., the intravitreal space. It should be understood that the terms "drug" and "agent" are used interchangeably herein throughout. In one variation, the drug reservoir is silicone oil-free (lacks silicone oil or one of its derivatives) and is not internally covered or lubricated with silicone oil, its derivative or a modification thereof, which ensures that silicone oil does not get inside the eye causing floaters or intraocular pressure elevation. In another variation, the drug reservoir is free of any lubricant or sealant and is not internally covered or lubricated with any lubricating or sealing substance, which ensures that the said lubricating or sealing substance does not get inside the eye causing floaters or intraocular pressure elevation.

**[0155]** In some variations, the reservoir is made of a material that contains a cyclic olefin series resin, a cyclic olefin ethylene copolymer including commercially available products such as Zeonex® cyclo olefin polymer (ZEON Corporation, Tokyo, Japan) or Crystal Zenith® olefinic polymer (Daikyo Seiko, Ltd., Tokyo, Japan) and APEL™ cyclo olefin copolymer (COC) (Mitsui Chemicals, Inc., Tokyo, Japan), a cyclic olefin ethylene copolymer, a polyethylene terephthalate series resin, a polystyrene resin, a polybutylene terephthalate resin, and combinations thereof. In one variation, it may be beneficial to use a cyclic olefin series resin and a cyclic olefin ethylene copolymer that have a high transparency, a high heat resistance, and minimal to no chemical interaction with a pharmacological product such as a protein, a protein fragment, a polypeptide, or a chimeric molecule including an antibody, a receptor or a binding protein.

**[0156]** Exemplary agents may be selected from classes such as anti-inflammatories (e.g., steroidal and non-steroidal), anti-infectives (e.g., antibiotics, antifungals, antiparasitics, antivirals, and antiseptics), cholinergic antagonists and agonists, adrenergic antagonists and agonists, anti-glaucoma agents, neuroprotection agents, agents for cataract prevention or treatment, anti-oxidants, antihistamines, anti-platelet agents, anticoagulants, antithrombics,

anti-scarring agents, anti-proliferatives, anti-tumor agents, complement inhibitors (e.g., anti-C5 agents, including anti-C5a and anti-C5b agents), vitamins (e.g., vitamin B and derivatives thereof, vitamin A, depaxapenthenol, and retinoic acid), growth factors, agents to inhibit growth factors, gene therapy vectors, chemotherapy agents, protein kinase inhibitors, tyrosine kinase inhibitors, PEGF (pigment epithelial growth factor), small interfering RNAs, their analogs, derivatives, conjugates, and modifications thereof, and combinations thereof.

**[0157]** Particular agent classes that may be useful include without limitation, anti-neovascularization agents, anti-VEGF agents, anti-PDGF agents, anti-vascular permeability agents, protein kinase C inhibitors, EGF inhibitors, tyrosine kinase inhibitors, steroidal anti-inflammatories, nonsteroidal anti-inflammatories, anti-infectives, anti-allergens, cholinergic antagonists and agonists, adrenergic antagonists and agonists, anti-glaucoma agents, neuroprotection agents, agents for cataract prevention or treatment, anti-proliferatives, anti-tumor agents, complement inhibitors, vitamins, growth factors, agents to inhibit growth factors, gene therapy vectors, chemotherapy agents, protein kinase inhibitors, small interfering RNAs, aptamers, antibodies or antibody fragments, growth factor receptors and receptor fragments, analogs, derivatives, and modifications thereof, and combinations thereof.

**[0158]** Non-limiting, specific examples of drugs that may be used alone or as part of a combination drug therapy include Lucentis™ (ranibizumab), Avastin™ (bevacizumab), Macugen™ (pegaptanib), steroids, e.g., dexamethasone, dexamethasone sodium phosphate, triamcinolone, triamcinolone acetonide, and fluocinolone, taxol-like drugs, integrin or anti-integrin agents, vascular endothelial growth factor (VEGF) trap (aflibercept) (VEGF receptor fragments or analogs), anecortave acetate (Retaane), and limus family compounds. Non-limiting examples of members of the limus family of compounds include sirolimus (rapamycin) and its water soluble analog SDZ-RAD, tacrolimus, everolimus, pimecrolimus, and zotarolimus, as well as analogs, derivatives, conjugates, salts, and modifications thereof, and combinations thereof.

**[0159]** Topical anesthetic agents may also be included in the reservoirs. For example, lidocaine, proparacaine, prilocaine, tetracaine, betacaine, benzocaine, ELA-Max®, EMLA® (eutectic mixture of local anesthetics), and combinations thereof may be used.

**[0160]** Some variations of the injection devices described herein include a filter that filters the contents of the reservoir as it is delivered into the eye. For example, the filter may be used to remove infectious agents and enhance sterility of an active agent formulation before injection into the eye. Thus, inclusion of a filter into the device may be useful because the eye is an immune-privileged site, and introduction of even a small quantity of pathogens such as bacteria may cause sight-threatening intraocular infection (endophthalmitis). The filter may also be used to remove impurities, e.g., silicone droplets, from an active agent formulation prior to injection into the eye. This may be useful for intraocular drugs because a small impurity injected into a subject's eye may result in the subject seeing it as floater(s) that may be intractable, which significantly worsens the quality of vision.

**[0161]** In one variation, the filter pore size is between about 0.2 μm (microns) and about 10 μm (microns), between about 0.2 μm (microns) to about 4 μm (microns), or between about 0.1 μm (microns) and about 500 μm (microns) to facilitate filtration of bacterial pathogens, particulate matter or impurities such as silicone droplets from the outgoing drug being injected intraocularly. Thickness of the said may range from between about 50 μm (microns) to about 250 μm (microns), or from between about 10 μm (microns) to about 10000 μm (microns).

**[0162]** The filter may be made from any suitable non-reactive material, such as a low protein-binding material. Exemplary filter materials include without limitation, thermoplastic fluoropolymers such as PVDF (polyvinylidene fluoride); mixed cellulose esters; nylons; polyesters; nitrocelluloses; acrylic polymers such as Versapor® acrylic copolymer; polyethersulfones such as found in Supor™ filters; a combination, a mixture, or a blend thereof.

**[0163]** The filter may be integrated with the device housing, the reservoir, the conduit, or any part of the device. In one variation, the filter is internal to the device. For example, the filter is configured to be inside the drug reservoir, or inside the conduit, or at the junction between reservoir and conduit. In another variation, filter is detachable or removable from the device. In one variation, the filter is located within the reservoir at its distal end. In another variation, the filter is located at the proximal end of the lumen of the conduit. The

filter may also be placed at any location within and along the lumen of the conduit, e.g., at its proximal end, in the middle, or at the distal end of the conduit.

**[0164]** The reservoirs and devices described here may be suitable for intraocular administration of a very small volume of a solution, suspension, gel or semi-solid substance. For example, a volume between about 1 µl and about 200 µl, or between about 10 µl and about 150 µl, or between about 20 µl and about 100 µl may be delivered. To that end, the device will generally have a very small "dead space," which enables intraocular administration of very small volumes.

**[0165]** The device reservoirs may be pre-loaded during the manufacturing process or loaded manually before the intraocular injection, as further described below.

Drug Loaders

**[0166]** Front loading of an injection device when the drug is loaded through the injection needle generally dulls the needle tip and removes at least some of the lubricant coating from the needle making it more difficult and uncomfortable for the needle to penetrate the target tissue. There is also a higher risk of contaminating the injection needle while manipulating it with a drug container. Back loading, for example through the plunger, often leads to wasting a significant amount of the drug, for example, more than 0.05-0.1 mL, which is undesirable with expensive agents, as well as when smaller drug volumes are used, as is typically the case for intravitreal injections. Here total volumes in the range of 0.05-0.1 ml are generally used. When a detachable needle is used, drug may be lost in the syringe luer and needle hub when the loading needle is exchanged with an injection needle, and contamination of the sterile drug conduit may occur. Thus, it would be beneficial to have a front-loading mechanism that allows for direct loading of the drug into drug reservoir without passing the drug through the tip of the drug conduit, exchanging or detaching the drug conduit, or losing a significant volume of the drug during the loading process.

**[0167]** In view of the above, when a drug or formulation is to be loaded into the reservoir of the devices described herein prior to intraocular injection, a loading member may be employed. The loading member may be removably attached to the distal end of the housing. For example, the loading member may function as a loading dock that quantitatively controls the volume of a liquid, semi-liquid, gelatinous, or suspension drug that is to be loaded into the device. For example, the loading member may comprise a dial mechanism (21) that

allows the operator to preset a particular volume of a drug to be loaded into the device (FIGS. 21 and 22). The loading may occur with a precision raging from about 0.01 µl and about 100 µl, or from about 0.1 µl and 10 µl. Such a loading member may allow for loading the device reservoir with a liquid, semi-liquid, gelatinous or suspended drug in a particular volume equal or less than that of the drug storage container, which allows for airless loading of the drug into the device. This may be beneficial because air injected into the eye will result in the sensation of seeing "floaters" by the patient, which may be uncomfortable and distracting to the patient particularly during driving or other similar activities.

**[0168]** As shown in FIG. 22, the drug loading mechanism (23) includes a wide base member (25) for upright loading of the reservoir (27) through its proximal (further from the eye) end (29). Also shown are exemplary front (31) and back (33) covers, as well as a dialable control mechanism (21) for setting the loading and/or injection volume(s). In other variations, the devices comprise a loading mechanism such as a loading dock (35A), wherein the dock (35A) interfaces with a drug storage container (FIGS. 25A-25B) such as a vial known to those skilled in the art and penetrates through the vial stopper to gain access to the drug contained inside the vial so that the drug could be loaded into the device reservoir. In FIGS. 25A-25B, the dock mechanism is located in the dependant position so that the drug vial (37) is positioned directly above the dock so that the drug moves from the vial downward in the direction of gravity.

**[0169]** In one variation, the dock mechanism comprises a needle or a sharp cannula that has openings or fenestrations (39) at its base. The said openings or fenestrations are positioned immediately adjacent to the internal aspect of the vial stopper when the loading dock penetrates into the drug vial while in the desired loading position, which in turn enables airless drug loading into the device as well as complete drug removal from the storage container. Airless drug loading may be beneficial because it may prevent the patient from seeing small intraocular air bubbles or "floaters." Complete drug removal is also beneficial given that small drug volumes and expensive medications are typically used.

**[0170]** In other variations, for example, when the devices have a flat side surface (FIGS. 24A-24D) or a flat front or back surface (FIG. 22), the loading mechanism includes a loading dock located 180 degrees from the flat surface. This results in a loading dock pointing straight upwards, which enables its penetration into a drug container in the dependent position, which in turn enables airless drug delivery into the device, as well as complete drug

removal from the storage container and its loading into the said device without drug retention and loss in the storage container.

**[0171]** In further variations, as shown in FIGS. 33A-33B, an access port (loading port) (144) may be provided at the distal end of the needle assembly (125) that allows drug from a storage container (146) to be loaded into the reservoir (122). Access port (144) may be placed at any suitable location on the needle assembly (125) or housing (102) to provide access to the reservoir. For example, if desired, the access port may be placed in the front wall (i.e., side or lateral wall) of the housing or even the ocular contact surface (not shown) so that drug loading occurs from the front of the device. The lateral access port may be configured to load drug through the wall of the device housing and into the reservoir in a manner that directs the drug toward the plunger seal and away from the internal opening of the injection needle. This way the small amount of the medication to be loaded does not get splashed over the front part of the drug reservoir. In some variations, the lateral access port is round or oval. When the access port is round, it may have a diameter ranging from between about 1.0 mm and 5.0 mm. The lateral access port may be positioned at about a 1 degree to about a 90 degree angle with respect to the axis of the plunger. With this orientation, direct visualization of drug loading may occur while moving the plunger.

**[0172]** Access port (144) may comprise a seal or a plug configured to seal the reservoir against air or fluid leak, and/or external bacterial contamination and may be made from any suitable material, e.g., silicone, rubber, or any soft thermoplastic polymer such as, but not limited to, polyurethane, Kraton™ styrenic block copolymers consisting of polystyrene blocks and rubber blocks, polyethylene, polypropylene, polyvinyl chloride, or combinations thereof that allows sealable penetration by a sharp conduit.

**[0173]** In some variations, the access port stopper or seal may comprise a fully or partially encircling sleeve. Here the sleeve may also serve as a finger grip or a holder. In another variation, and as shown in FIGS. 52A-52C, the injection device (1400) may include an H-shaped stopper or plug (1402) for sealing the access port (1404) that provides access through the housing wall (1406) of the device (1400) into the reservoir (1408). An opening (1410), e.g., in the wall of a needle assembly (1412) that contains the reservoir (1408), may be provided so that drug loading may occur through the access port (1404) and opening (1410) into the reservoir (1408). Here the H-shaped stopper or plug (1402) is flush with the internal surface of the reservoir (1408) when it is inserted to seal the access port (1404).

**[0174]** One or multiple membranes (148) may also be provided, e.g., in the ocular contact surface (108) to seal the internal compartment of the housing against air leak and/or external bacterial contamination. For example, the thickness of the membrane or the combined plurality of membranes may range from about 0.025 mm to about 5.0 mm, or range from about 0.1 mm to about 1 mm. One or multiple small apertures (150) may also be included in the wall of the housing (102) to help control air outflow from the housing (102). The number and diameter of the apertures (150) may be varied to control the rate of (needle assembly and) needle deployment.

**[0175]** In some variations, e.g., when a pneumatic actuation mechanism is used, drug loading may be controlled by a drug-loading piston. For example, as shown in FIG. 38, the device (400) may include a drug-loading piston (402) having a proximal end (404) and a distal end (406). The distal end (406) is adapted to include a threaded portion (408). Thus, during loading of a drug from container (410) through adaptor (412) and access port (414), the drug-loading piston (402) can be rotated and withdrawn to create negative pressure within the reservoir (416). This negative pressure in turn draws the drug through the needle (418) and into the reservoir (416). A receptacle (420) may also be provided at the distal end of the device for holding initially loaded drug prior to transfer into the reservoir (416).

**[0176]** Some variations of the drug loading devices include a filter that filters the contents of the drug container as it is delivered into the reservoir. For example, the filter may be used to remove infectious agents and enhance sterility of an active agent formulation before delivery into the reservoir. Thus, inclusion of a filter into the drug loader may be useful because the eye is an immune-privileged site, and introduction of even a small quantity of pathogens such as bacteria may cause sight-threatening intraocular infection (endophthalmitis). The filter may also be used to remove impurities, e.g., silicone droplets, from an active agent formulation as it is transferred to the reservoir and prior to injection into the eye. This may be useful for intraocular drugs because a small impurity injected into a subject's eye may result in the subject seeing it as floater(s) that may be intractable, which significantly worsens the quality of vision.

**[0177]** In one variation, the filter pore size is between about 0.2 μm (microns) and about 10 μm (microns) to facilitate filtration of bacterial pathogens from the outgoing drug being injected intraocularly. In another variation, the filter pore size is between about 0.1 μm (microns) and about 500 μm (microns) to facilitate filtration of particulate matter or

impurities such as silicone droplets from the outgoing drug being injected intraocularly. In yet a further variation, the filter pore size is between about 0.2 μm (microns) to about 4.0 μm (microns). Thickness of the said filter may range from between about 50 μm (microns) to about 250 μm (microns), or from between about 10 μm (microns) to about 10000 μm (microns).

**[0178]** The filter may be made from any suitable non-reactive material, such as a low protein-binding material. Exemplary filter materials include without limitation, thermoplastic fluoropolymers such as PVDF (polyvinylidene fluoride); mixed cellulose esters; nylons; polyesters; nitrocelluloses; acrylic polymers such as Versapor® acrylic copolymer; polyethersulfones such as found in Supor™ filters; a combination, a mixture, or a blend thereof.

**[0179]** The filter may be integrated with the drug loading device housing, the reservoir, a conduit, or any suitable part of the device. In another variation, filter is detachable or removable from the device. In one variation, the filter is located within the reservoir at its distal end. In another variation, the filter is located at the proximal end of the lumen of the conduit. The filter may also be placed at any suitable location within and along the lumen of the conduit, e.g., at its proximal end, in the middle, or at the distal end of the conduit.

Actuation Mechanisms

**[0180]** The devices described here generally include an actuation mechanism within the housing that deploys the conduit from the housing and enables the delivery of drug from the device into the intraocular space. In other variations, the conduit is deployed by an actuation mechanism contained within a separate cartridge that can be removably attached to the device housing, e.g., using snap-fit or other interlocking elements. The actuation mechanisms may have any suitable configuration, so long as they provide for accurate, atraumatic, and controlled delivery of drug into the intraocular space. For example, the actuation mechanisms may deliver a drug or formulation into the eye by way of intraocular injection at a rate ranging from about 1 μl/sec to about 1 ml/sec, from about 5 μl/sec to about 200 μl/sec, or from about 10 μl/sec to about 100 μl/sec. The actuation mechanisms may generally provide a force of needle deployment that is strong enough to penetrate the eye wall comprising the conjunctiva, sclera and the pars plana region of the ciliary body, but less than that causing damage to the intraocular structures due to high velocity impact. This force

depends on several physical factors, including but not limited to, the needle gauge utilized, the speed/rate of needle deployment at the point of contact between the needle tip and the eye wall which in turn determines the impact force. An exemplary range of force that may be generated by the actuation mechanisms is about 0.1 N (Newton) to about 1.0 N (Newton). The velocity of needle deployment may also range between about 0.05 seconds and about 5 seconds.

**[0181]** In some variations, the actuation mechanism is a single-spring mechanism. In other variations, the actuation mechanism is a two-spring mechanism. In further variations, the actuation mechanism is pneumatic, e.g., employing negative pressure such as vacuum, or a positive pressure driven mechanism. In further variations, the actuation mechanism is driven magnetically or electrically, e.g., by a piezo-electric or magnetic rail mechanism. These types of actuation mechanisms may be configured to allow independent control of the rate and force of drug injection (controlled, e.g., by the first spring member in the two-spring variation), and the rate and force of the dispensing member deployment (controlled, e.g., by the second spring member in the two-spring variation). Exemplary two-spring mechanisms are shown in FIGS. 26 and 27.

**[0182]** FIG. 28 also depicts an exemplary integrated intraocular drug delivery device with a two-spring actuation mechanism. In FIG. 28, the device (100) includes a housing (102) having a proximal end (104) and a distal end (106). An ocular contact surface (108) is attached to the distal end (106). A measuring component (110) is attached to one side of the ocular contact surface (108). As further described below, a trigger (112) that is operatively coupled to the housing (102) works with the first spring (114) and the second spring (116) of the actuation mechanism to deploy pins (118) through openings (120) in the housing (102), to thereby deliver drug from the reservoir (122). First spring (114), second spring (116), pins (118), openings (120), and reservoir (122) are better shown in FIG. 29. Also in FIG. 29, a conduit, e.g., needle (124), is depicted within the housing in its first non-deployed state. Needle (124) is configured as being part of an assembly (125) such that movement of the assembly results in corresponding movement of the needle (124). A stop (115) is provided at the proximal end (127) of the assembly (125), which is connected to the distal end of the first spring (114) and the proximal end of the second spring (116). The springs, as well as other components of the device may be connected via medical grade adhesives, friction or snap fit, etc.

**[0183]** In FIG. 30, the second spring (116) is operatively connected to a plunger (132) by friction fit within a compartment (134) of the plunger (132). In the pre-activated state, as shown in FIG. 29, the plunger (132) and second spring (116) are held in place by pins (118). The pins (118) are removably engaged to the plunger (132) at plunger groove (138), and lock the plunger (132) in place via friction fit against the plunger groove (138) and housing (102).

**[0184]** Activation of the first spring (114) of the actuation mechanism by activating the trigger deploys the needle (124) into the intraocular space, i.e., it moves the needle (124) from its first non-deployed state (FIG. 29) to its second deployed state (FIG. 30). Referring to FIGS. 30 and 31A-31C, activation of the first spring (114) occurs by depression of trigger (112) by, e.g., one or two fingers, which also depresses buttons (126). As shown in FIGS. 31A and 31B, buttons (126) are configured with a button groove (128) that allows the buttons (126) to align with channels (130) in the housing (102). Once aligned with the channels (130), the buttons (126) may be slidingly advanced along the channels (130). The channels may be of any suitable length. The distance from the distal end of the channel to the distal end of the housing may range from about 10 to about 20 mm. In one variation, the distance from the distal end of the channel to the distal end of the housing is about 16 mm. The rate of movement along the channels (130) may be controlled manually by the user, automatically controlled by the force of spring expansion, or a combination of both. This movement of the buttons (126) allows expansion of the first spring (114) against stop (115) so that the needle assembly (125) and needle (124) can be deployed. The channels in the housing may have any suitable configuration. For example, as shown in FIG. 31C, the channels (130) may be spiral cut within the housing to allow rotation or a corkscrew type movement of the needle upon advancement, which may facilitate needle penetration through the eye wall.

**[0185]** Activation of the first spring (114) will typically result in activation of the second spring (116) to deliver drug out of the device and into the intraocular space. For example, as shown in FIG. 30, the expansion force of first spring (114) against stop (115) that is also connected to the proximal end of the second spring (116) works to expand the second spring (116) so that the assembly (125) is advanced within the housing (102). As illustrated in FIGS. 32A-32C, when the pins (118) that are removably engaged to plunger (132) reach openings (120), they are deployed out through the openings (120). Expulsion of the pins (118) from the device, then allows free expansion of the second spring (116) against plunger (132), to thereby push drug residing with reservoir (122) out of the device. The openings

(120) may be covered by a membrane or seal (140) that can be penetrated by the pins (118) to give a visual indication that the drug has been delivered.

**[0186]** A two-spring actuation mechanism, as shown in FIGS. 41A-41B may also be used. Referring to FIG. 41A, integrated device (600) includes an actuation mechanism comprising a first spring (602) and a second spring (604). In use, when trigger (606), e.g., a lever, is depressed, first spring (602) is released to advance shaft (608) in the direction of the arrow, which in turn advances needle (610) out of the tip of the device (600). Continued advancement of the shaft (608) advances the injection sleeve (612) and top seal (614) so that drug within reservoir (616) may be delivered through needle (610). Referring to FIG. 41 B, once the drug has been injected, tabs (618) removably engage housing openings (620) to thereby release second spring (604), which then moves shaft (608) backward to retract needle (610) (not shown).

**[0187]** In some variations, a single-spring actuation mechanism is employed, as shown in FIGS. 36 and 37. When a single spring is used, the actuation mechanism is configured much like the two-spring mechanism described above except that the second spring is removed. Thus, in its pre-activated state, as shown in FIG. 36, a device (300) with a single spring (302) may activate the single spring (302) by depression of trigger (304) by, e.g., one or two fingers, which also depresses buttons (306). The buttons (306) are configured with a button groove (308) that allows the buttons (306) to align with channels (not shown) in the housing (310). Once aligned with the channels, the buttons (306) may be slidingly advanced along the channels. This movement of the buttons (306) allows expansion of the spring (302) against plunger (312) so that the needle assembly (314) and needle (316) can be deployed. When the pins (318) that are removably engaged to plunger (312) reach openings (320) within the housing (310), they are deployed out through the openings (320). Expulsion of the pins (318) from the device, then allows further expansion of the spring (302) against plunger (312), to thereby push drug residing with reservoir (322) out of the device. Although not shown here, the openings (320) may be covered by a membrane or seal that can be penetrated by the pins (318) to give a visual indication that the drug has been delivered.

**[0188]** A pneumatic actuation mechanism may also be employed. In one variation, as depicted in FIGS. 34 and 35A and 35B, the pneumatic actuation mechanism includes a plunger, pins, and housing openings in the same fashion as described for the single- and two-spring mechanisms. However, instead of using a spring to deploy the needle assembly and

plunger, a piston is used to slidingly advance the needle assembly within the housing. For example, in FIG. 34, a device with a pneumatic actuation mechanism (200) includes a piston (202) and trigger (204). The piston (202) is used to compress air into the housing (206) of the device (202). If desired, the amount of compressed air the piston includes in the device may be controlled by a dial or other mechanism (not shown). The proximal end of the housing may also be configured, e.g., with a flange, crimps, or other containment structure, that allows translational movement of the piston (202) into the housing but not out of the housing. Upon depression of a trigger (208), a pair of locking pins (210) are also depressed to thereby allow the compressed air generated by the piston (202) to push the needle assembly (212) forward. This advancement of the needle assembly (212) deploys the needle (214) out of the device (FIG. 35B). As previously stated, pins (216) similar to those above that lock the plunger (218) in place are also provided. Upon their expulsion from the device out of openings (220) in the housing (206) due to forward movement of the needle assembly (212), the compressed air further moves the plunger (218) forward to thereby push drug residing with reservoir (222) out of the device. Rotational pins (224) may also be included, which upon release by the sliding needle assembly (212) allow rotation of the needle assembly (212) with respect to the housing (206).

**[0189]** As previously stated, a trigger may be coupled to the housing and configured to activate the actuation mechanism. In one variation, the trigger is located on the side of the device housing proximate the device tip at the ocular interface surface (e.g., the distance between the trigger and device tip may range between 5 mm to 50 mm, between 10 mm to 25 mm, or between 15 mm to 20 mm), so that the trigger can be activated by a fingertip while the device is positioned over the desired ocular surface site with the fingers on the same hand. In another variation, the trigger is located on the side of the device housing at 90 degrees to the measuring component, so that when the ocular contact surface is placed on the eye surface perpendicular to the limbus, the trigger can be activated with the tip of the second or third finger of the same hand that positions the device on the ocular surface.

**[0190]** Some variations of the device may include a control lever for initiating plunger movement. In these instances, the control lever may actuate the plunger in a mechanical manner, e.g., by spring-actuation, similar to that described above. In other variations, actuation of the plunger may occur through a combination of mechanical and manual features. For example, the initiation of plunger movement may be aided by a manual force

applied onto the control lever, while a spring-actuated mechanism for generating a mechanical force is also employed to move the plunger forward inside the device barrel to inject drug. In instances where the control lever is connected to the plunger, the initiation of plunger movement and drug injection is controlled by the manual component, whereas the rate of fluid injection is controlled by the mechanical force. Here a reduced manual force may be applied to the plunger due to its combination with a co-directional mechanical force, thus facilitating the stability of device positioning on the ocular surface at a precise injection site.

**[0191]** The control lever may be placed between 10 mm and 50 mm from the tip of the device that interfaces with the eye surface, or between 20 mm and 40 mm from the tip of the device. Positioning of the control lever in this manner may enable atraumatic and precise operation of the device with one hand.

**[0192]** As illustrated in FIGS. 43A-43D, exemplary integrated device (700) includes a housing (702), a dynamic sleeve (704) slidable thereon, an ocular contact surface (706), a plunger (708), and a control lever (710) for manually actuating the plunger (708) to inject drug through needle (712). An expanded sectional view of the ocular contact surface (706), dynamic sleeve (706), plunger (708), and needle (712) shown in FIG. 43 A is shown in FIG. 43B. In use, after placing the ocular contact surface (706) on the eye, the applied pressure may automatically slide the dynamic sleeve (704) back (in the direction of the arrow) to expose the needle and allow needle penetration through the eye wall. The control lever (710) may then be slidably advanced manually (in the direction of the arrow in FIG. 43C) to advance plunger (708). When injection of the drug through the needle (712) is complete, the dynamic sleeve (704) may be slidably advanced manually to cover the needle, as shown in FIG. 43D.

**[0193]** The dynamic sleeve may be slidably advanced or retracted manually by a fine mobility control mechanism, also referred to as a mobility control mechanism. In these instances, the dynamic sleeve may comprise a high-traction surface located on the outer surface of the sleeve, which may aid movement of the sleeve with a fingertip. In one variation, the high-traction surface may be engraved or contain markings with a serrated pattern. In other variations, as shown in FIG. 45A, a platform or pad (e.g., a fingertip pad) (900) may be attached to the outer surface of the sleeve (902) to help manually advance or retract the sleeve. The platform or pad may also include a high-traction surface (904), the

perspective, side, and top views of which are illustrated in FIGS. 45B, 45C, and 45D, respectively. Platform or pad (900) will typically include a base (912) for attachment to the sleeve (902). Base (912) may be of any suitable configuration. For example, the base of the platform or pad may be configured as a cylinder (FIG. 45H) or with a narrowed portion (portion of lesser diameter), such as a dumbbell or apple core shape (FIG. 45I). In yet further variations, the fine mobility control mechanism is configured as raised, circular flange located at or near the proximal edge of the dynamic sleeve. In one example, the circular flange is raised about 1 mm to about 1.5 mm over the outer surface of the dynamic sleeve, so that the operator has a tactile feel of its surface, and is able to control movement of the sleeve when applying a retractive (pulling) or pushing force to it.

**[0194]** Some variations of the devices described herein include a grip having a retraction slot or channel that works in combination with the dynamic resistance component to inject drug into the eye. Referring to FIG. 45 A, grip (906) may be a component coupled (usually fixedly attached) to the device housing (908) at the proximal end (912) of the sleeve (902). The grip (906) may be configured to include a retraction slot (910) in its wall. In use, when the sleeve (902) is retracted, as shown by the direction of the arrow in FIG. 45J, the base (912) of the pad or platform is moved into the slot (910). The retraction slot (910) may be configured as a channel of uniform width (FIG. 45F), or as a channel with a keyhole-type configuration, e.g., having a narrowed portion (FIG. 45G) or enlarged portion (FIG. 45E) at the slot proximal or distal end. The retraction slot may provide sensory feedback, e.g., when the endpoint of retraction is reached. The configuration of the base of the platform or pad may be chosen so that it provides a friction fit with the slot. For example, when the slot has a narrowed portion, the base may also have a narrowed portion.

**[0195]** When grips are employed, the devices may also include a locking mechanism. In one variation, when the end point of the sleeve retraction and needle exposure/deployment is reached, the wide portion of the sleeve slot is aligned with the wide portion of a grip slot and with an opening in the housing and an opening in the plunger shaft, allowing the platform base to be inserted into the plunger shaft to lock it relative to the platform that become an actuation lever for manual drug injection. The narrow part of the base enters the narrow part of the sleeve slot, which unlocks the platform relative to the sleeve allowing its movement towards device tip. In another variation, when the platform base reaches the end point of the retraction slot, it may be depressed into an opening in the plunger shaft and becomes a

locking pin to connect the platform and the plunger. When it is depressed, its narrow portion enters the keyhole-shaped slot in the sleeve, and becomes movable within the slot moving towards the tip of the sleeve (unlocks the platform base and sleeve).

**[0196]** The mobility control mechanism may be beneficial when the user desires to control the amount of pressure exerted by the device tip on the eye surface in order to deploy the needle during its intraocular penetration. With a mobility control mechanism, the user may use a fingertip to either reduce or increase counter-forces that regulate the sleeve movement and needle exposure.

**[0197]** For example, if the user exerts the pulling force onto the said high-traction surface (that is pulling the high-traction surface of the sleeve away from the device tip), this movement may facilitate needle exposure and reduce the amount of pressure force (down to 0 Newton) needed to be applied to the eye wall in order to slide the sleeve back and expose the needle. In another variation, if the user exerts a pushing force (that is pushing the high-traction surface of the sleeve towards the device tip), this movement may counteract and impedes needle exposure, which may allow the device tip to apply increased pressure to the eye wall prior to the initiation of sleeve movement and needle exposure.

**[0198]** In use, the platform or pad may be slid with a second or third finger. Again, this allows the injector to manually modulate the sleeve resistance and movement along the device tip. For example, by pushing the pad and thus the sleeve forward with a fingertip, the injector provides some resistance at the beginning of the procedure when the device tip is being positioned on the eye surface (and the needle needs to remain completely covered). Then the injector would release his/her fingertip from the sleeve pad to enable needle deployment and its transscleral penetration. Some variations of the device may also include a step or a ring-shaped ridge at the end of the sleeve path, so that after the sleeve is pulled back past this step, it would automatically trigger spring-actuated plunger movement. The fingertip pad could be used to pull the sleeve back past the said step at the end of needle deployment in order to actuate the plunger movement and drug injection.

**[0199]** When a platform or pad is employed, it may reduce the amount of pressure the device exerts on the eyeball before the sleeve begins to move to expose the needle, and thus, allow customization of the amount of applied pressure from patient to patient.

**[0200]** In another aspect, the dynamic sleeve may provide gradual needle exposure as it penetrates through the eye wall so that the needle is exposed 1 mm or less when it meets most resistance at the eye surface. Here the rest of the needle is located inside the sleeve with at least its most distal unexposed point or a longer segment being protected inside the narrow exit orifice or canal. Such sleeve design may minimize the risk of needle bending compared to the conventional syringe with a long exposed needle. This design may enable the utilization of smaller a gauge needle without increased risk of it being bent as it penetrated through the eye wall. The smaller needle gauge may render it more comfortable and less traumatic during its intraocular penetration.

**[0201]** Some variations of the devices described here may comprise an endpoint shock absorber. The endpoint shock absorber may be a component that cushions the eye against the force transmitted by the dynamic sleeve and the needle when they come to an abrupt stop. The transmitted force wave may be harmful for the delicate structures inside the eye such as the lens, retina and the choroidal vasculature. Inclusion of an endpoint shock absorber may allow the needle to come to a soft and gradual stop at the end of its deployment path when it is fully extended through the eye wall into the intraocular cavity. In one variation, the shock absorber is provided as a tapered surface at the distal end or distal portion of the dynamic sleeve. In another variation, the shock absorber is a soft sleeve located at the base of the drug conduit (such as at the hub of an injection needle). Here the soft sleeve may be configured to contact the tip of the device when the needle is fully deployed. In yet another variation, the shock absorber is the soft tip of the device, where the soft tip is configured to contact the hub of the needle when the needle is fully deployed. Exemplary materials suitable to make the endpoint shock absorbers include without limitation, methylmethacrylate (MMA); polymethylmethacrylate (PMMA); polyethylmethacrylate (PEM) and other acrylic-based polymers; polyolefins such as polypropylene and polyethylene, vinyl acetates, polyvinylchlorides, polyurethanes, polyvinylpyrollidones, 2-pyrrolidones, polyacrylonitrile butadiene, polycarbonates, polyamides, fluoropolymers such as polytetrafluoroethylene (e.g., TEFLON™ polymer); polystyrenes; styrene acrylonitriles; cellulose acetate; acrylonitrile butadiene styrene; polymethylpentene; polysulfones; polyesters; polyimides; natural rubber; polyisobutylene rubber; polymethylstyrene; silicone; and derivatives, copolymers and blends thereof.

**[0202]** The devices desribed herein may also include a visual feedback mechanism configured to allow the operator to precisely determine when the needle has been deployed to the desired extent, and to safely initiate drug injection. Furthermore, during the needle deployment process, the eyes of the operator should be pointed at the device tip-eye interface. Thus, it would be beneficial for the visual feedback mechanism to be located in close proximity to the device tip-eye interface, so as not to distract the operator from closely monitoring the device position during the entire intraocular drug delivery procedure. With such a configuration, the operator does not have to take his/her eyes off of the device-ocular interface during the entire injection procedure, minimizing the risk of accidental trauma during unexpected movement of the eye or head of the subject. In some variations, the visual feedback mechanism may be coupled to a mechanical stopper at the end-point of the needle deployment process. Here the visual feedback mechanism may be configured as an elongated measuring tip band, where the tip comes up to a stop against the needle base or hub, which determines the end-point of needle deployment when the sleeve has been fully retracted. Another example of the visual feedback mechanism is a band or a spacer placed on the needle base, so that the band comes up to a stop against the inside surface of the tip, which determines the end-point of needle deployment when the sleeve has been fully retracted.

**[0203]** The devices described herein may be integrated or non-integrated. An exemplary injection device is shown in FIG. 48. In the figure, injection device (1100) comprises a housing (1101) having a wall (1106), a proximal end (1102), a distal end (1104), and a lumen (not shown) extending between the proximal end (1102) and distal end (1104). A plunger (1108) is slidable at least partially through the lumen. A longitudinally extending channel (1110) having a proximal end (1109) and a distal end (1111) formed through the wall (1106) is provided at the device distal end (1104). A plunger actuation lever such as knob (1112) is configured so that slidable advancement of the knob (1112) from the channel proximal end (1109) to the channel distal end (1111) also slidably advances the plunger (1108) to deliver medication into the eye. The channels may be of any suitable length. The distance from the distal end of the channel (1111) to the distal end of the housing (1104) may range from about 10 to about 20 mm. In FIG. 48, the distance from the distal end of the channel (1111) to the distal end of the housing (1104) is about 16 mm. The injection device of FIG. 48 also includes a cover or sleeve (1114) that overlays an opening or aperture in the housing wall (not shown) through which a drug loader (as previously described) may be placed. The drug loader would deliver medication from a drug vial to the reservoir of the device. The cover or

sleeve (1114) may partially, substantially or entirely surround the housing and be made from materials such as rubber or silicone. The drug loader may puncture the cover or sleeve and extend through the opening or aperture of the housing so that medication can be filled into the reservoir.

**[0204]** In FIG. 48, the injection device also includes a flange (1116). As previously described, flange (1116) may be part of a fine mobility control mechanism. The flange (1116) may be configured as a raised, circular flange located at or near the proximal edge of a dynamic sleeve (1118). As shown in more detail in FIG. 49B, dynamic sleeve (1118) has a first section (1120) and a second section (1122). The inner diameter of first section (1120) will typically be greater than the inner diameter of second section (1122). For example, the inner diameter of the first section may be about 7.0 mm and the inner diameter of the second section may be about 4.8 mm. The length of the first and second sections may also vary. In FIG. 49B, the length of the first section (1120) may be about 9.0 to 10 mm and the length of the second section (1122) may be about 9.0 to 10 mm. A ramped portion (1124) may also connect the first and second portions (1120 and 1122). Ramped portion (1124) may be configured so that an angle is created with the longitudinal axis (1126) of the device, e.g., an angle of 30 degrees as shown in FIG. 49B.

**[0205]** The injection device of FIG. 48 also includes a sectoral measuring component (1128). The sectoral measuring component in this as well as other variations has a circumference (that spans 360 degrees) and a longitudinal axis. Radially extending members such as tabs or spokes may be provided around the circumference of the sectoral measuring component in any suitable manner, e.g., equidistant from each other, symmetrically or asymmetrically spaced around the circumference, but typically in a manner that avoids contact with the eyelid(s) and eyelashes to maintain its sterility. Thus, the radially extending members will generally be provided on a section (portion) of the circumference and will generally span a certain number of degrees of arc around the circumference. For example, and as specifically shown in FIG. 50, sectoral measuring component (1200) has a section (1202) having three radially extending members (1204). The section (1202) spans an area (e.g., arc) around the circumference of 90 degrees. In this configuration, the radially extending members are spaced around the circumference 45 degrees apart from each other. In another variation, as shown in FIG. 51, sectoral measuring component (1300) is configured

similarly to that illustrated in FIG. 50 except that the distal ends of the radially extending members (1302) are rounded.

II. METHODS

**[0206]** Methods for using the integrated intraocular drug delivery devices are also described herein. In general, the methods include the steps of positioning an ocular contact surface of the device on the surface of an eye, applying pressure against the surface of the eye at a target injection site using the ocular contact surface, and delivering an active agent from the reservoir of the device into the eye by activating an actuation mechanism. The steps of positioning, applying, and delivering are typically completed with one hand.

**[0207]** The application of pressure against the surface of the eye using the ocular contact surface may also be used to generate an intraocular pressure ranging between 15 mm Hg to 120 mm Hg, between 20 mm Hg to 90 mm Hg, or between 25 mm Hg to 60 mm Hg. As previously stated, the generation of intraocular pressure before deployment of the dispensing member (conduit) may reduce scleral pliability, which in turn may facilitate the penetration of the conduit through the sclera, decrease any unpleasant sensation on the eye surface during an injection procedure, and/or prevent backlash of the device. Intraocular pressure control may be generated or maintained manually or automatically using pressure relief valves, pressure sensors, pressure accumulators, pressure sensors, or components such as slidable caps having locking mechanisms and/or ridges as previously described.

**[0208]** Use of the devices according to the described methods may reduce pain associated with needle penetration through the various covers of the eye wall such as the conjunctiva that is richly innervated with pain nerve endings. The anesthetic effect at the injection site during an intraocular injection procedure may be provided by applying mechanical pressure on the conjunctiva and the eye wall over the injection site before and/or during the needle injection. The application of mechanical pressure to the eye wall may also transiently increase intraocular pressure and increase firmness of the eye wall (and decrease its elasticity), thereby facilitating needle penetration through the sclera. Furthermore, the application of mechanical pressure to the eye wall may displace intraocular fluid within the eye to create a potential space for the drug injected by the device.

**[0209]** The devices may be used to treat any suitable ocular condition. Exemplary ocular conditions include without limitation, any type of retinal or macular edema as well as

diseases associated with retinal or macular edema, e.g., age-related macular degeneration, diabetic macular edema, cystoid macular edema, and post-operative macular edema; retinal vascular occlusive diseases such as CRVO (central retinal vein occlusion), BRVO (branch retinal vein occlusion), CRAO (central retinal artery occlusion), BRAO (branch retinal artery occlusion), and ROP (retinopathy of prematurity), neovascular glaucoma; uveitis; central serous chorioretinopathy; and diabetic retinopathy.

**[0210]** When dexamethasone sodium phosphate solution is used to treat an ocular condition, the dose of dexamethasone sodium phosphate that may be administered into the eye by each individual injection device may range between about 0.05 mg and about 5.0 mg, between about 0.1 mg and about 2.0 mg, or between about 0.4 mg and about 1.2 mg.

**[0211]** In some variations, a topical anesthetic agent is applied on the ocular surface before placement of the device on the eye. Any suitable topical anesthetic agent may be used. Exemplary topical anesthetic agents include without limitation, lidocaine, proparacaine, prilocaine, tetracaine, betacaine, benzocaine, bupivacaine, ELA-Max®, EMLA® (eutectic mixture of local anesthetics), and combinations thereof. In one variation, the topical anesthetic agent comprises lidocaine. When lidocaine is used, it may be provided in a concentration raging from about 1% to about 10%, from about 1.5% to about 7%, or from about 2% to about 5%. In another variation, the topical anesthetic agent is mixed with phenylephrine or another agent that potentiates or/and prolongs the anesthetic effect of the pharmaceutical formulation. The topical anesthetic agent may be provided in any suitable form. For example, it may be provided as a solution, gel, ointment, etc.

**[0212]** An antiseptic agent may also be applied on the ocular surface before placement of the device on the eye. Examples of suitable antiseptic agents include, but are not limited to, iodine, povidone-iodine (betadine®), chlorhexidine, soap, antibiotics, salts and derivatives thereof, and combinations thereof. The antiseptic agent may or may not be applied in combination with a topical anesthetic agent. When the antiseptic comprises povidone-iodine (Betadine®), the concentration of povidone-iodine may range from about 1% to about 10%, from about 2.5% to about 7.5%, or from about 4% to about 6%.

**[0213]** During the drug delivery process, the devices described here may be configured so that the injection needle enters the eye at the right angle that is perpendicular to the eye wall

(sclera). In other instances, the device may be configured so that the injection needle enters through the cornea into the anterior chamber of the eye parallel to the iris plane.

III. SYSTEMS AND KITS

**[0214]** Systems and kits that include the intraocular drug delivery devices are also described herein. The kits may include one or more integrated drug delivery devices. Such devices may be preloaded with an active agent. When a plurality of preloaded devices are included, they may be separately packaged and contain the same active agent or different active agents, and contain the same dose or different doses of the active agent.

**[0215]** The systems and kits may also include one or more separately packaged devices that are to be manually loaded. If the devices are to be manually loaded prior to use, then one or more separately packaged active agents may be incorporated into the kit. Similar to the preloaded device system or kit, the separately packaged active agents in the systems and kits here may be the same or different, and the dose provided by each separately packaged active agent may be the same or different.

**[0216]** Of course, the systems and kits may include any combination of preloaded devices, devices for manual loading, and active agents. It should also be understood that instructions for use of the devices will also be included. In some variations, one or more separately packaged measuring components may be provided in the systems and kits for removable attachment to the devices. Topical anesthetic agents and/or antiseptic agents may also be included.

IV. EXAMPLES

**[0217]** The following example serves to more fully describe the manner of using the above-described intraocular injection devices. It is understood that this example in no way serves to limit the scope of the invention, but rather is presented for illustrative purposes.

Example 1: Resistance Force Generated By the Dynamic Sleeve

**[0218]** An intraocular injection device comprising a 30-gauge needle covered by a dynamic sleeve (a bi-tapered design with each end of the sleeve tapered) was fixed onto an Imada tensile testing bed and moved against an Imada 10 N force gauge at a rate of 10 mm/minute. The resistance force was measured while the sleeve was pushed back to expose the needle

simulating the movement of the sleeve in practice. This produced a "U"-shaped force plotted against the sleeve displacement curve, as shown in FIG. 46. The resistance force at the beginning and the end of sleeve movement path was greater than that in the middle of the path. In FIG. 46, the illustrated range of resistance force generated may be between zero Newton and about 2 Newton or between about 0.1 Newton and about 1.0 Newton.

**[0219]** In one instance, the resistance force at the beginning of the sleeve path equaled the force required for the 30- or 31-gauge needle to penetrate through the human sclera (e.g., between 0.2 Newton and 0.5 Newton). When a using a higher-resistance sleeve was employed, the resistance force at the beginning of the sleeve path was greater than the force required for the 30- or 31-gauge needle to penetrate through the human sclera (e.g., over 1 Newton). However, the force was low enough to be comfortable for the patient and avoid potential damage to the eye (e.g., to avoid increase in intra-ocular pressure over 60 mmHg). In the middle portion of the sleeve movement path, the force approached zero Newton.

# CLAIMS

1. An injection device for intraocular drug delivery comprising:

a housing sized and shaped for manipulation with one hand, the housing having a proximal end and a distal end;

a resistance band at least partially surrounding the housing having a thickness between about 0.01 mm to about 5 mm;

a dynamic resistance component having proximal end and a distal end;

an ocular contact surface at the housing distal end;

a conduit at least partially within the housing, the conduit having a proximal end, a distal end, and a lumen extending therethrough; and

an actuation mechanism coupled to the housing and operably connected to the conduit and a reservoir for holding an active agent.

2. The injection device of claim 1, wherein the actuation mechanism comprises a slidable control lever.

3. The injection device of claim 1, further comprising a measuring component coupled to the distal end of the dynamic resistance component.

4. The injection device of claim 3, wherein the measuring component is a sectoral measuring component having a central core, the central core having a circumference and comprising a plurality of radially extending members.

5. The injection device of claim 4, wherein the radially extending members are configured to span between 1 degree and 180 degrees of arc around the circumference of the central core.

6. The injection device of claim 4, wherein the radially extending members are configured to span between 45 degrees and 90 degrees of arc around the circumference of the central core.

7. The injection device of claim 3, wherein the measuring component is configured to rotate about the longitudinal axis of the device.

8. The injection device of claim 1, wherein the dynamic resistance component comprises a dynamic sleeve.

9. An integrated device for intraocular drug delivery comprising:

a housing sized and shaped for manipulation with one hand, the housing having a proximal end and a distal end;

a sectoral measuring component coupled to a distal end of the device, the central core having a circumference and comprising a plurality of radially extending members;

a conduit at least partially within the housing, the conduit having a proximal end, a distal end, and a lumen extending therethrough;

an actuation mechanism coupled to the housing and operably connected to the conduit and a reservoir for holding an active agent; and

a dynamic resistance component.

10. The integrated device of claim 9, wherein the radially extending members are configured to span between 1 degree and 180 degrees of arc around the circumference of the central core.

11. The integrated device of claim 9, wherein the radially extending members are configured to span between 45 degrees and 90 degrees of arc around the circumference of the central core.

12. The integrated device of claim 9, wherein the sectoral measuring component is configured to rotate about the longitudinal axis of the device.

13. An injection device for intraocular drug delivery comprising:

a housing sized and shaped for manipulation with one hand, the housing having a wall, a proximal end and a distal end;

an ocular contact surface at the housing distal end;

a conduit at least partially within the housing, the conduit having a proximal end, a distal end, and a lumen extending therethrough;

an actuation mechanism coupled to the housing and operably connected to a reservoir for holding an agent;

a dynamic resistance component; and

a filter coupled to the device,

wherein the filter is configured to lie within the reservoir or the conduit, or at a junction between the reservoir and the conduit.

14. The injection device of claim 13, wherein the filter comprises a filter material having a pore size ranging from about 0.1 μm to about 50 μm.

15. The injection device of claim 13, wherein the filter material has a pore size ranging from about 0.2 μm to about 4.0 μm.

16. The injection device of claim 13, wherein the active agent is selected from the group consisting of anti-neovascularization agents, anti-VEGF agents, anti-PDGF agents, anti-vascular permeability agents, protein kinase C inhibitors, EGF inhibitors, tyrosine kinase inhibitors, steroidal anti-inflammatories, nonsteroidal anti-inflammatories, anti-infectives, anti-allergens, cholinergic antagonists and agonists, adrenergic antagonists and agonists, anti-glaucoma agents, neuroprotection agents, agents for cataract prevention or treatment, anti-proliferatives, anti-tumor agents, complement inhibitors, vitamins, growth factors, agents to inhibit growth factors, gene therapy vectors, chemotherapy agents, protein kinase inhibitors, small interfering RNAs, aptamers, antibodies or antibody fragments, growth factor receptors and receptor fragments, analogs, derivatives, and modifications thereof, and combinations thereof.

17. The injection device of claim 13, wherein the active agent is selected from the group consisting of ranibizumab, bevacizumab, VEGF-trap, VEGF receptor fragments or analogs, pegaptanib, dexamethasone, dexamethasone sodium phosphate, triamcinolone, triamcinolone acetonide, fluocinolone, taxol-like drugs, aflibercept, anecortave acetate, and limus family compounds.

18. The injection device of claim 13, wherein the dynamic resistance component comprises a dynamic sleeve.

19. The injection device of claim 13, further comprising a resistance band wholly or partially surrounding the housing.

20. The injection device of claim 13, wherein the filter is provided within the reservoir.

21. The injection device of claim 13, wherein the filter is provided within the conduit.

22. The injection device of claim 13, wherein the device comprises an access port in the wall of the housing.

23. The injection device of claim 22, wherein the device comprises a stopper for sealing the access port.

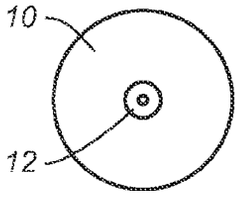



FIG. 1A

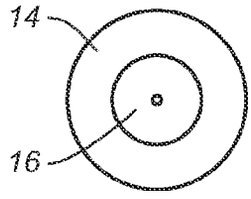



FIG. 1B

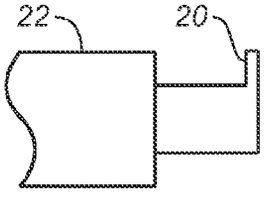



FIG. 2A

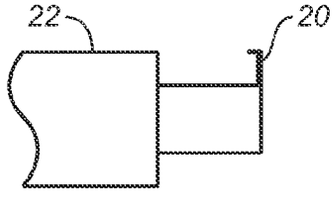



FIG. 2B

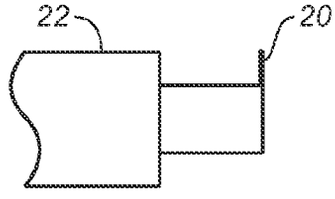



FIG. 2C

FIG. 3A1

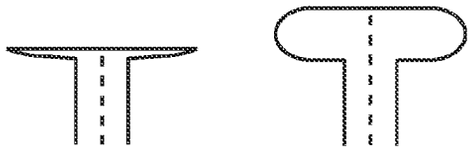


FIG. 3B1

FIG. 3A2

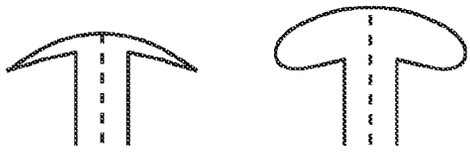


FIG. 3B2

FIG. 3A3

FIG. 3B3

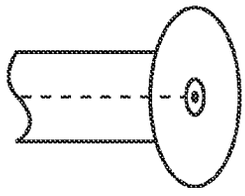


FIG. 4A

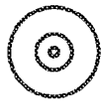


FIG. 4B1

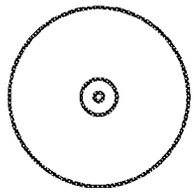


FIG. 4B2

FIG. 5A1

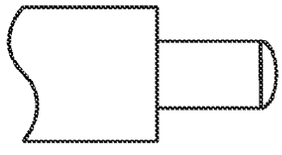


FIG. 5B1

FIG. 5A2

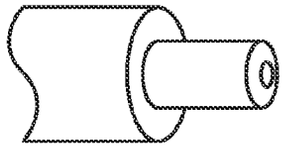


FIG. 5B2

FIG. 6A1

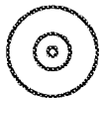
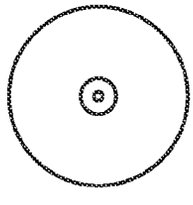


FIG. 6A2

FIG. 6B1



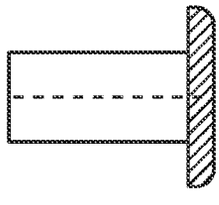


FIG. 6B2

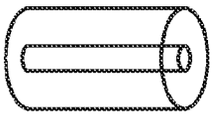
FIG. 7A1 

 FIG. 7A2

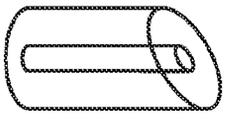
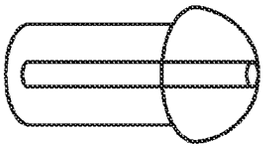
FIG. 7B1 

 FIG. 7B2

FIG. 7C1 

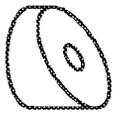
 FIG. 7C2

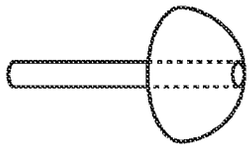
FIG. 7D 

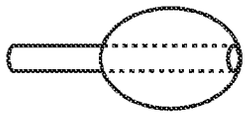
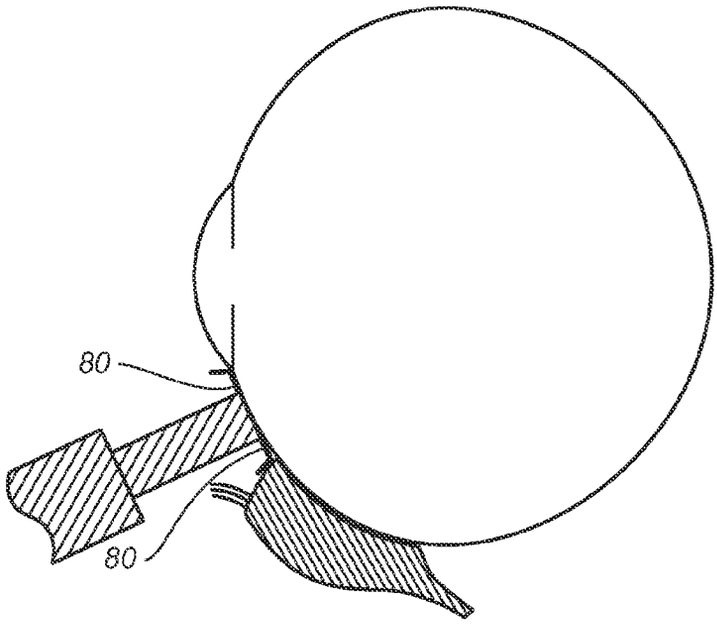
FIG. 7E 

FIG. 8



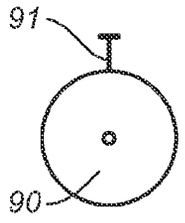



FIG. 9A

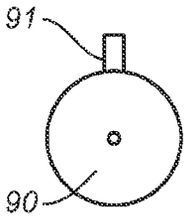



FIG. 9B

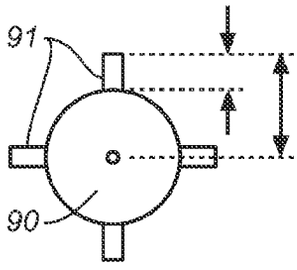



FIG. 9C

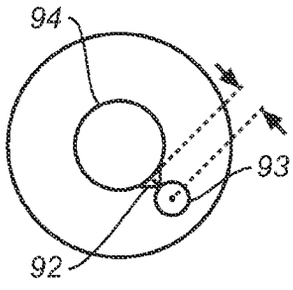



FIG. 10A

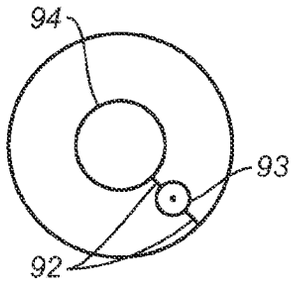



FIG. 10B

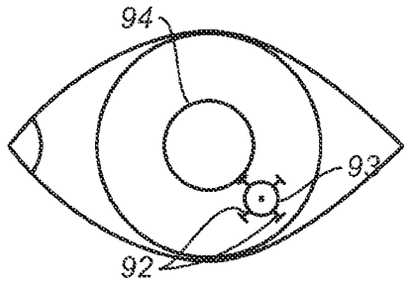



FIG. 10C

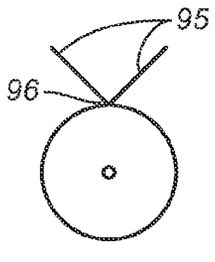



FIG. 11A

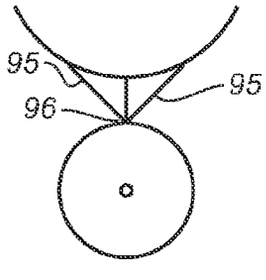



FIG. 11B

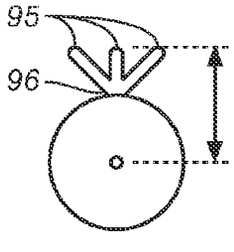



FIG. 11C

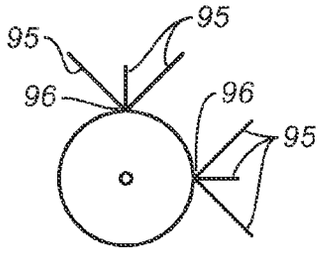



FIG. 11D

FIG. 12

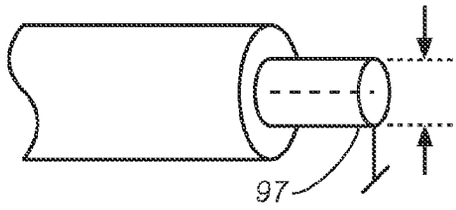



FIG. 13

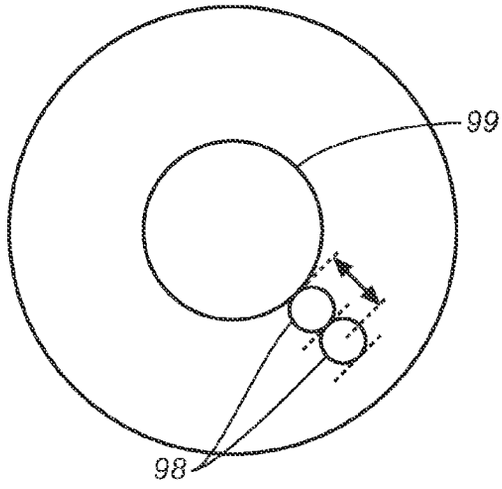



FIG. 14A

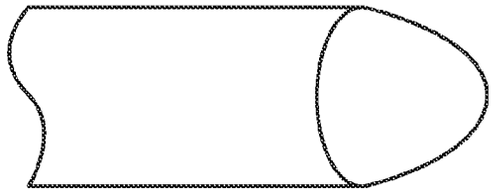


FIG. 14B

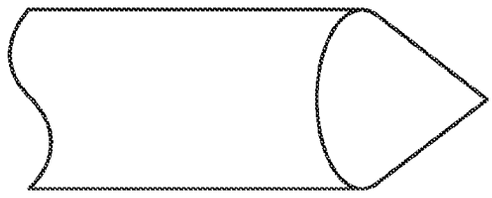


FIG. 14C

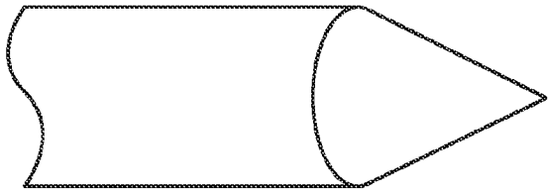


FIG. 15A1

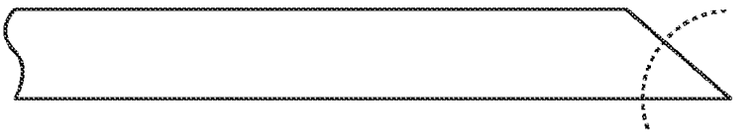


FIG. 15A2

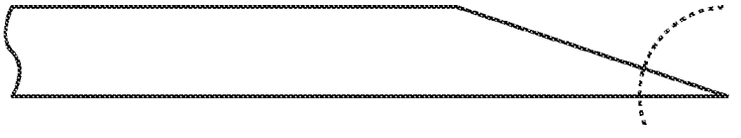


FIG. 16A

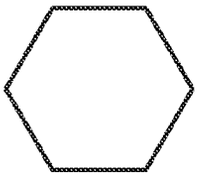


FIG. 16C

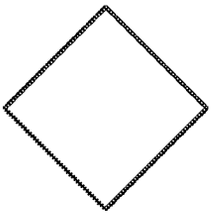


FIG. 16B

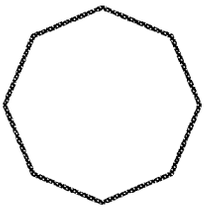
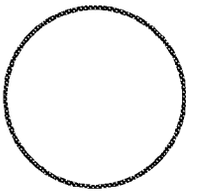


FIG. 16D



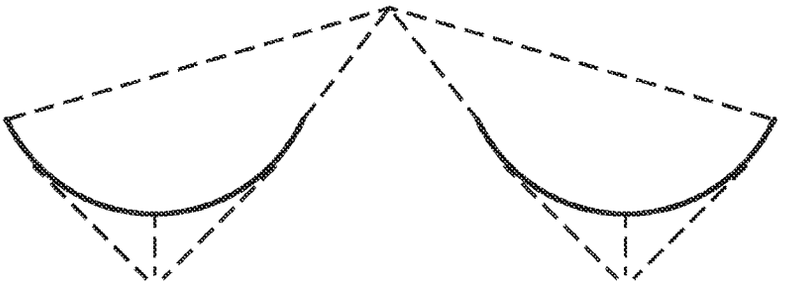


FIG. 17

FIG. 18A

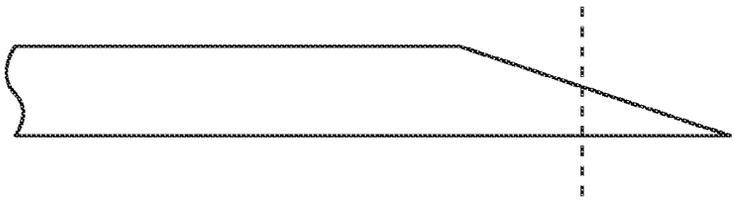
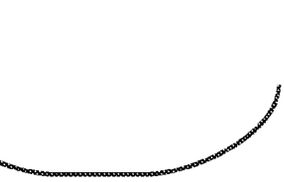


FIG. 18B

FIG. 18C



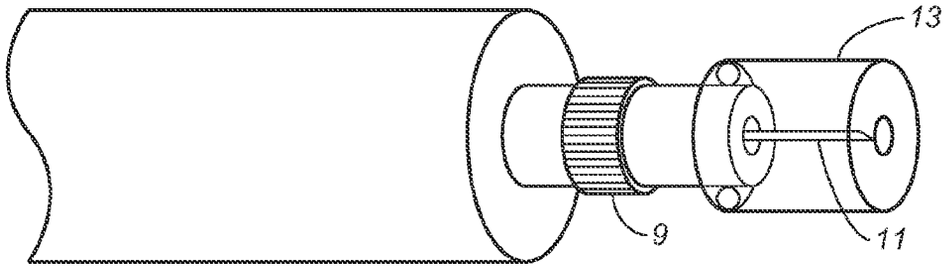



FIG. 19

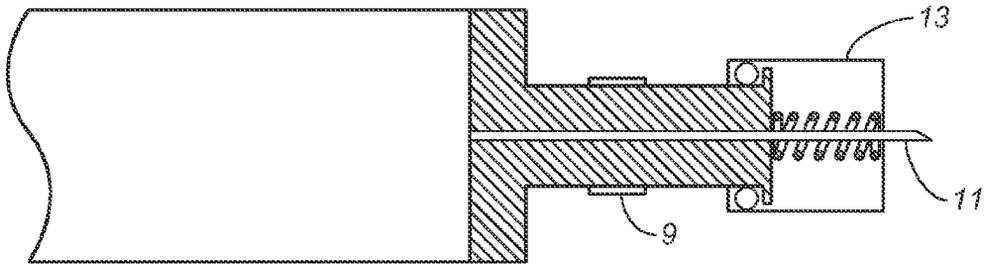



FIG. 20

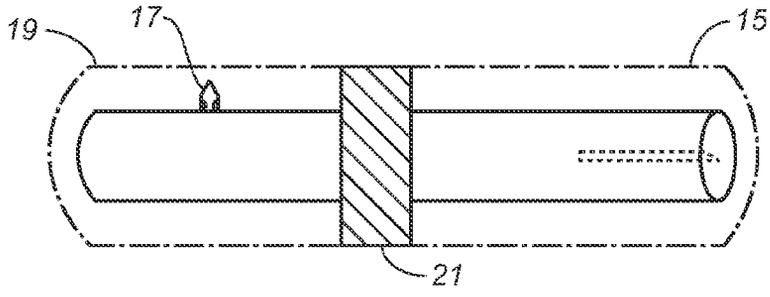



FIG. 21

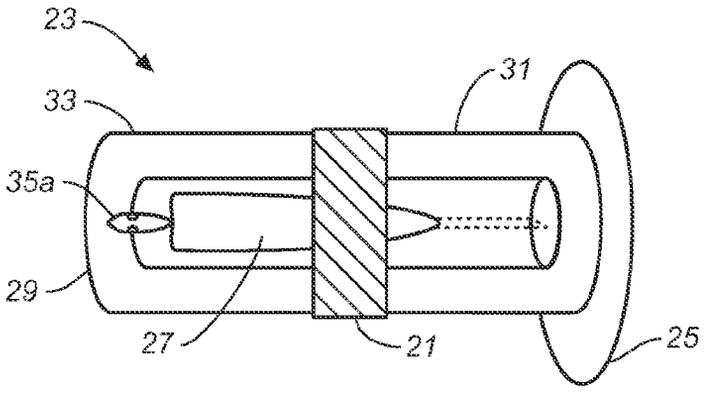



FIG. 22

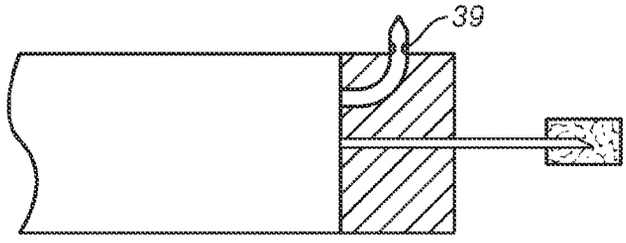



FIG. 23A

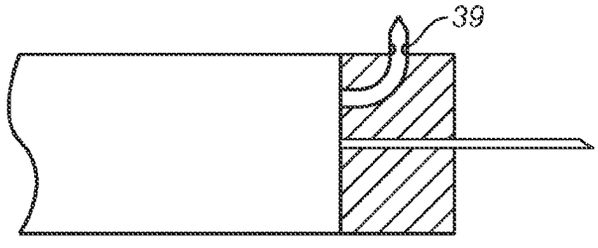



FIG. 23B

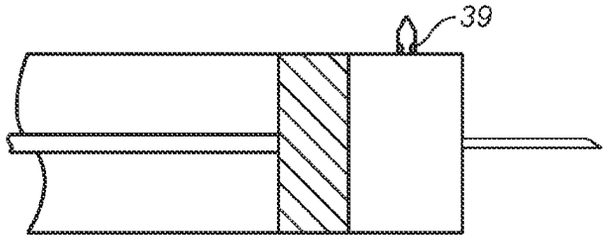



FIG. 23C

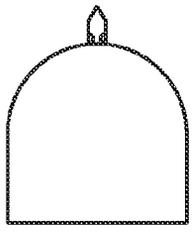


FIG. 24A

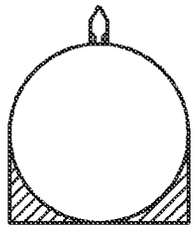


FIG. 24B

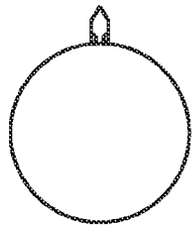


FIG. 24C

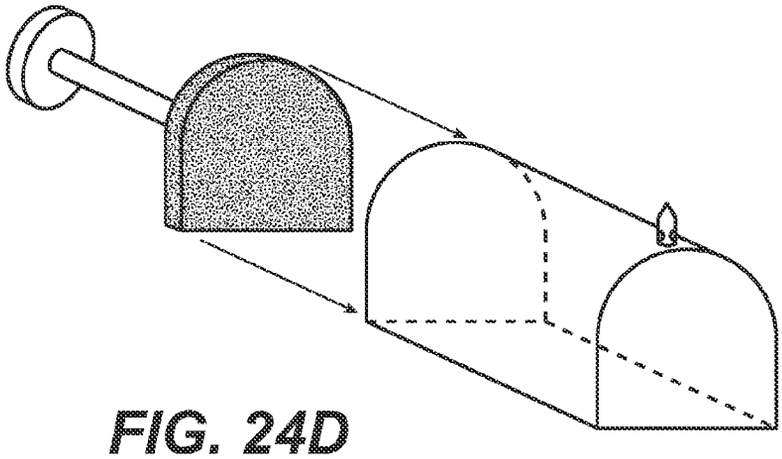


FIG. 24D

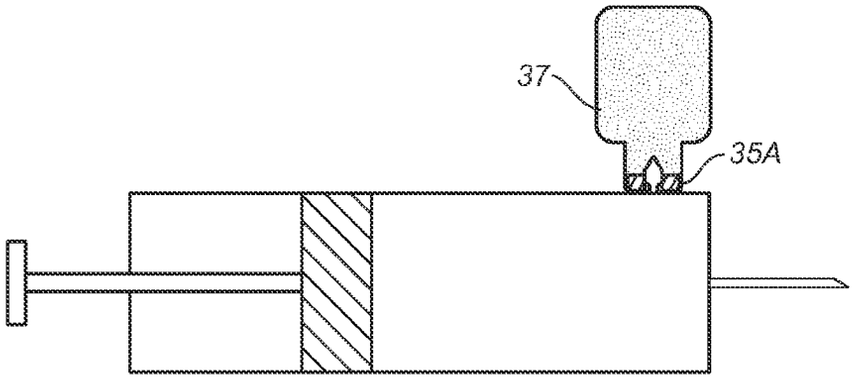



FIG. 25A

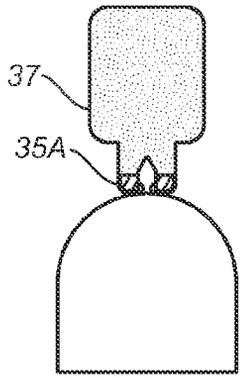



FIG. 25B

FIG. 26A

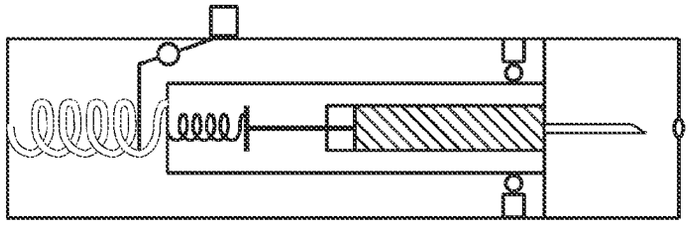


FIG. 26B

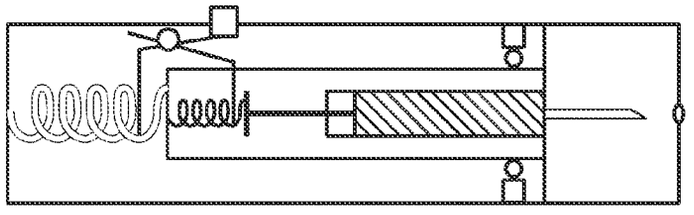


FIG. 26C

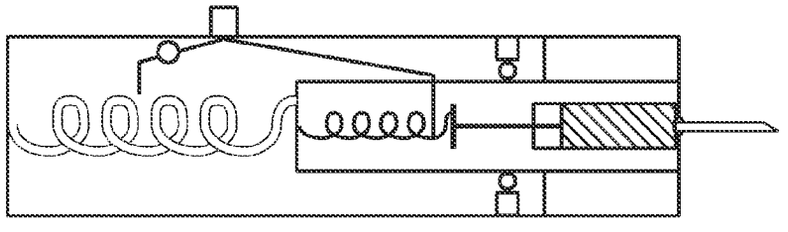
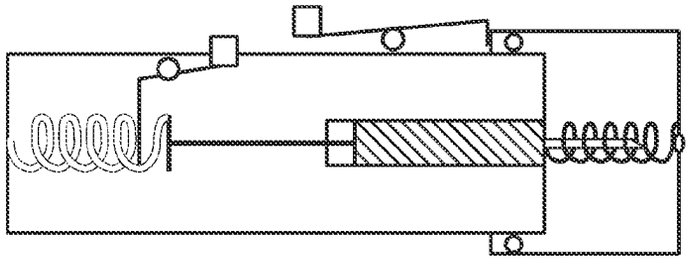


FIG. 27



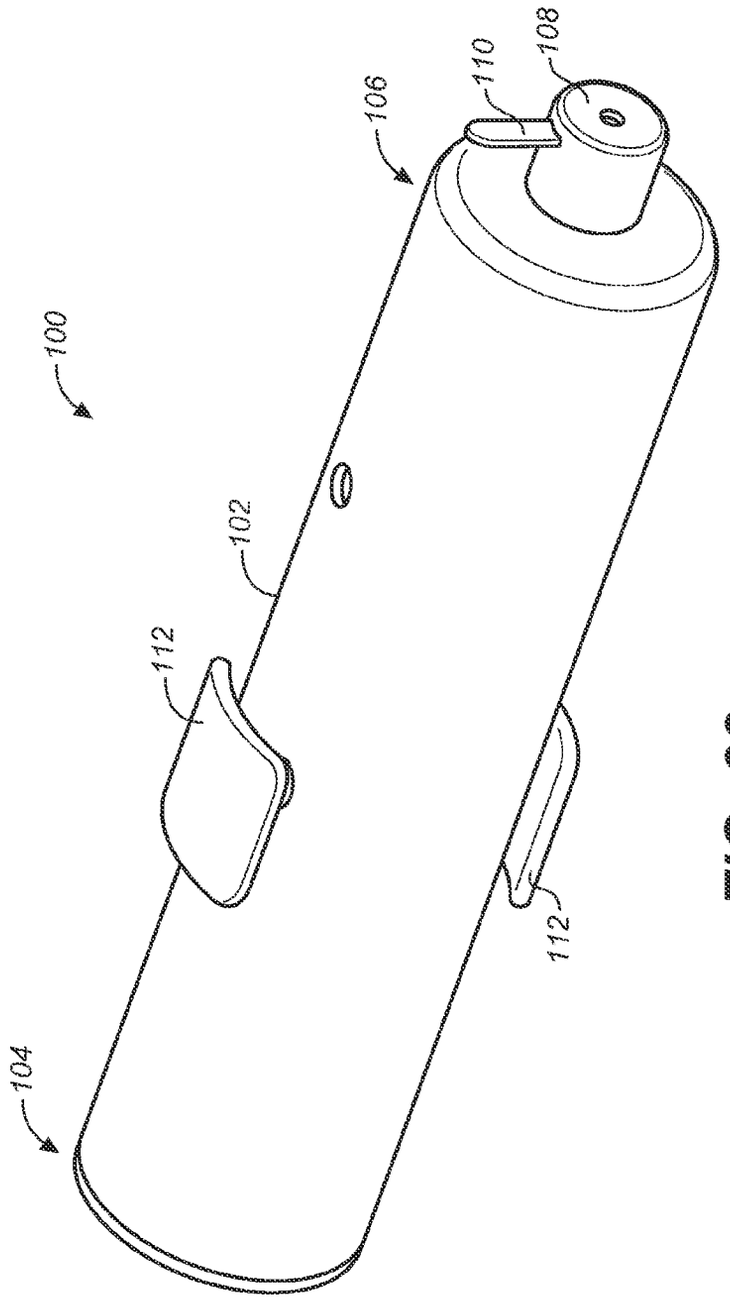



FIG. 28

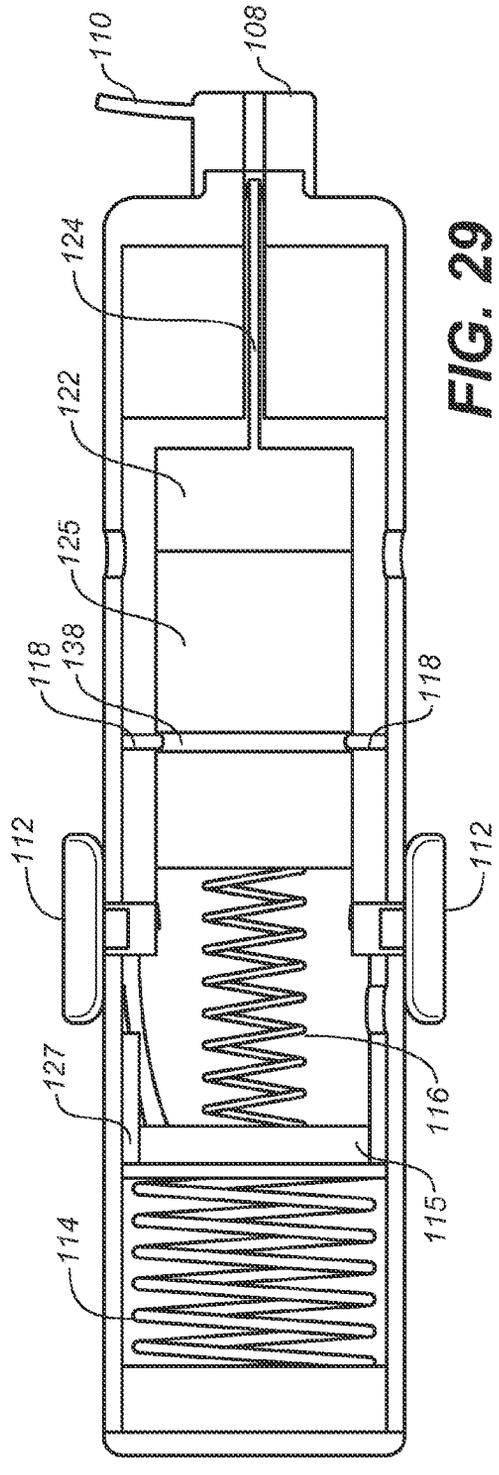



FIG. 29

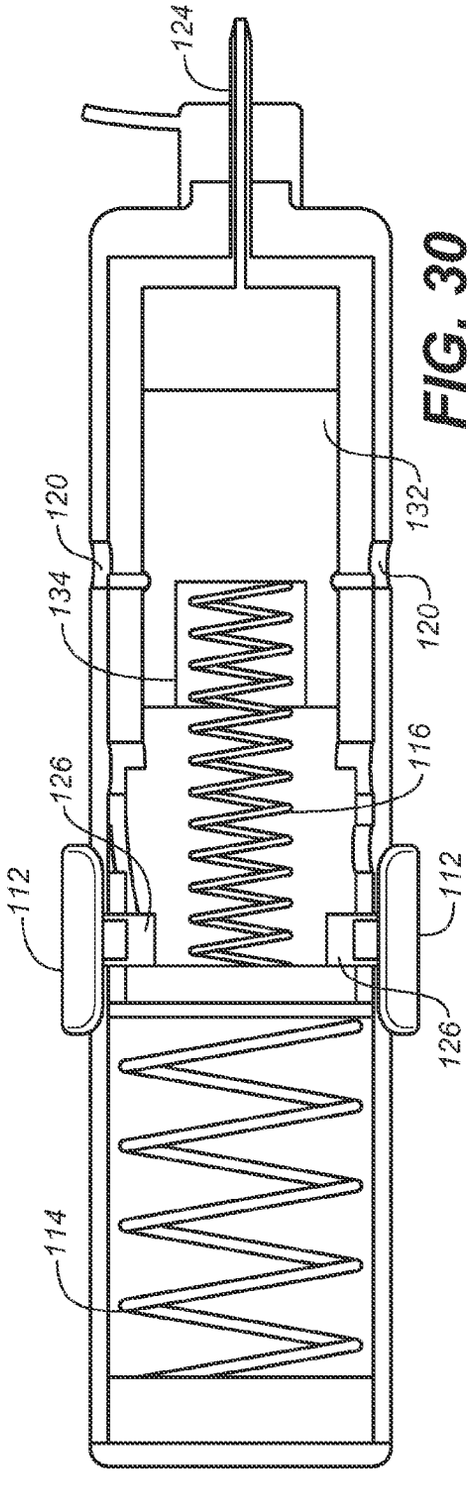



FIG. 30

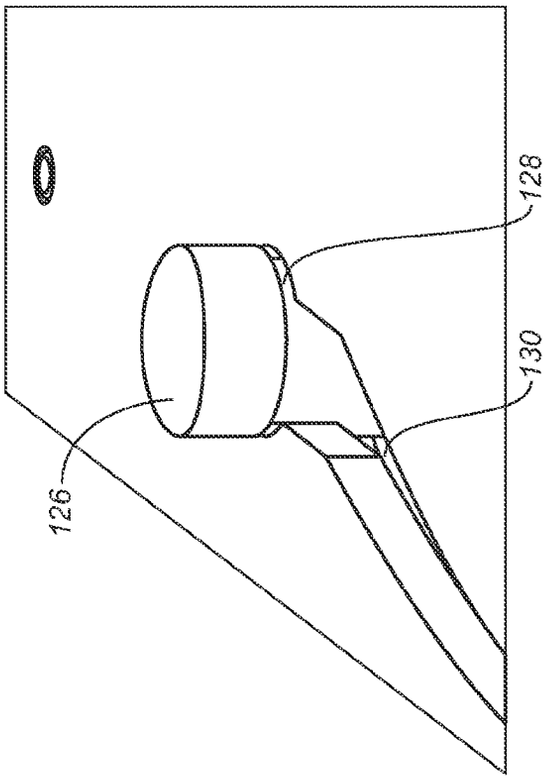



FIG. 31B

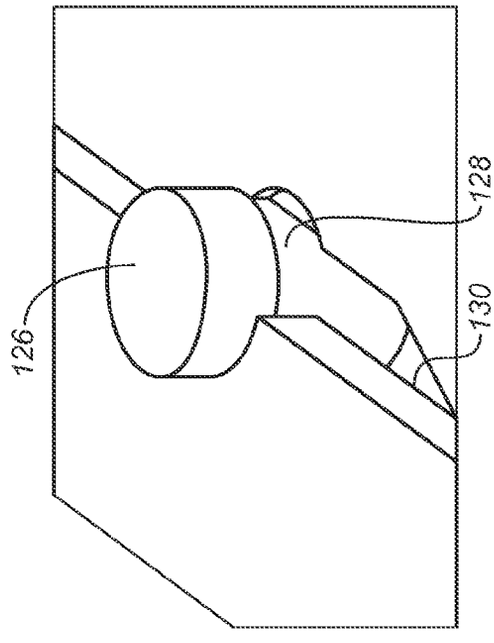



FIG. 31A

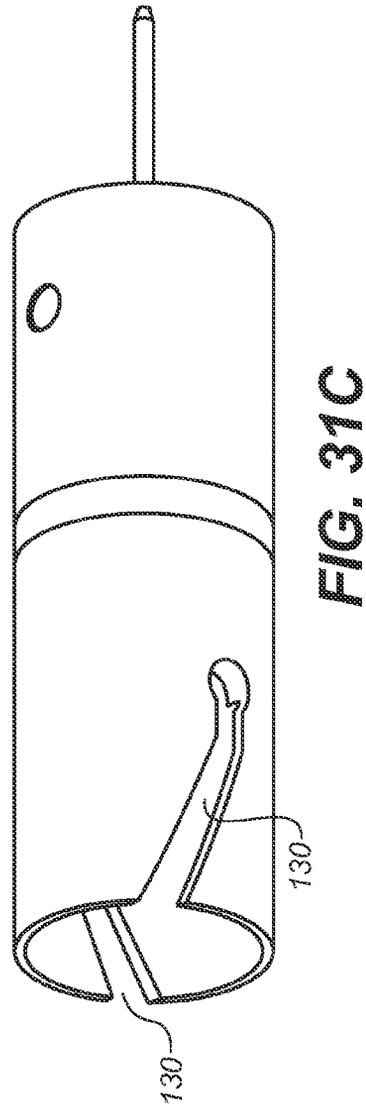



FIG. 31C

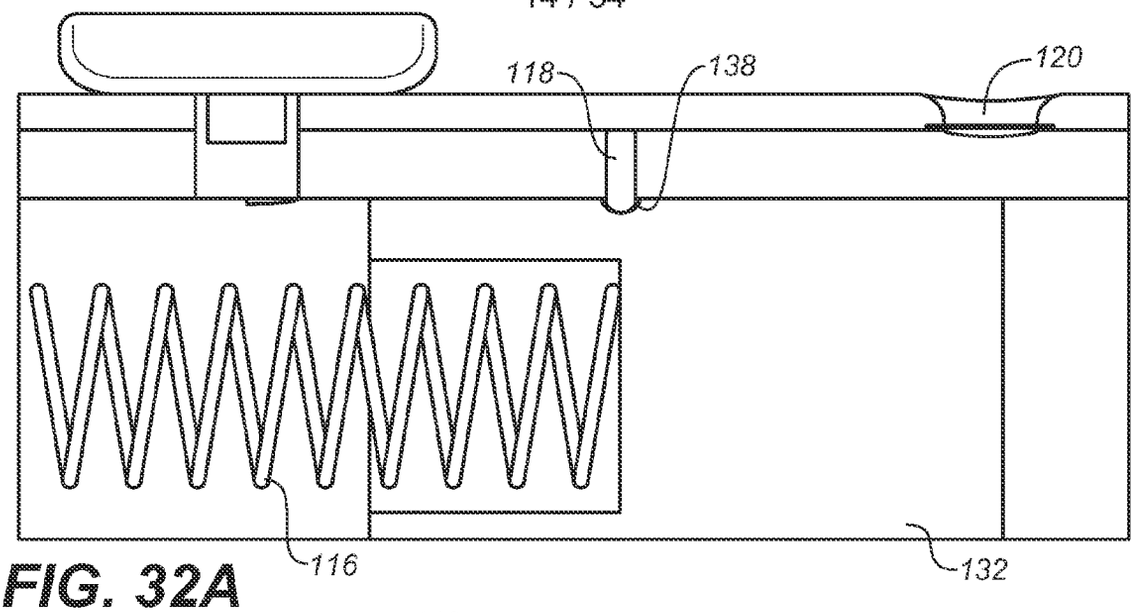



FIG. 32A

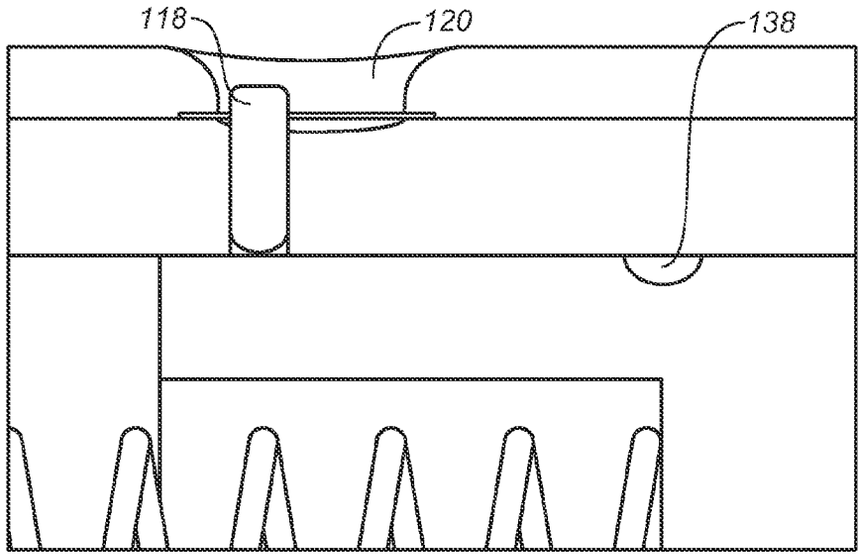



FIG. 32B

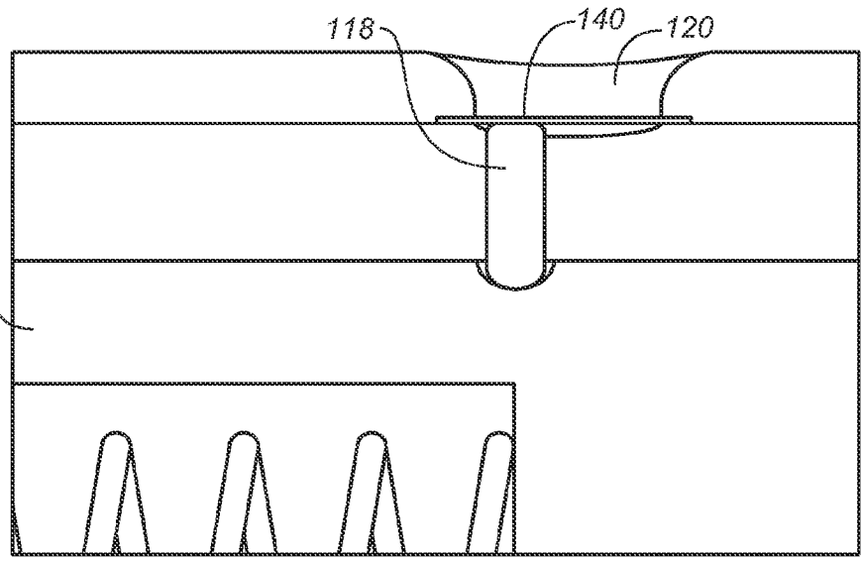



FIG. 32C

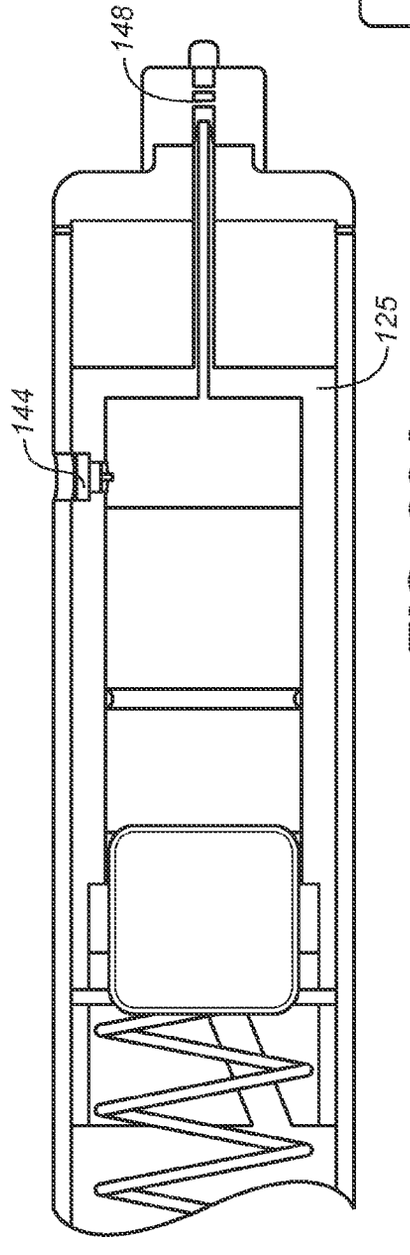



FIG. 33A

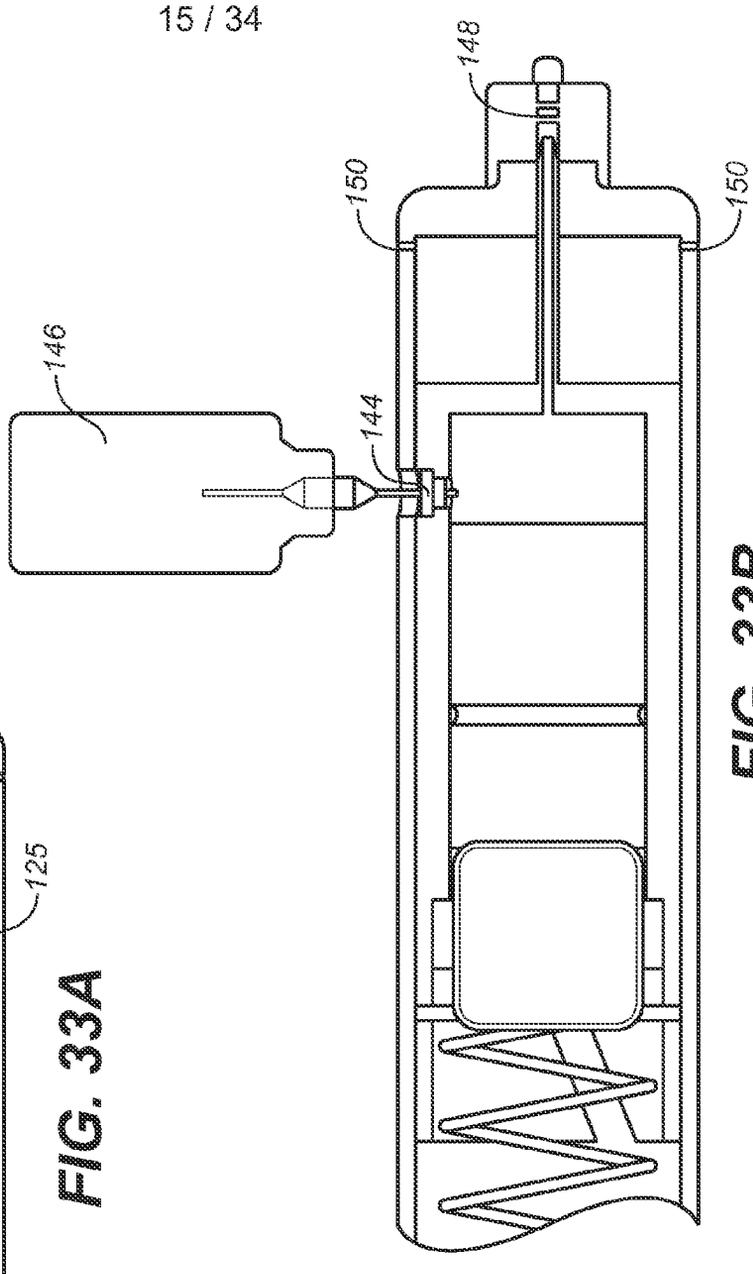



FIG. 33B

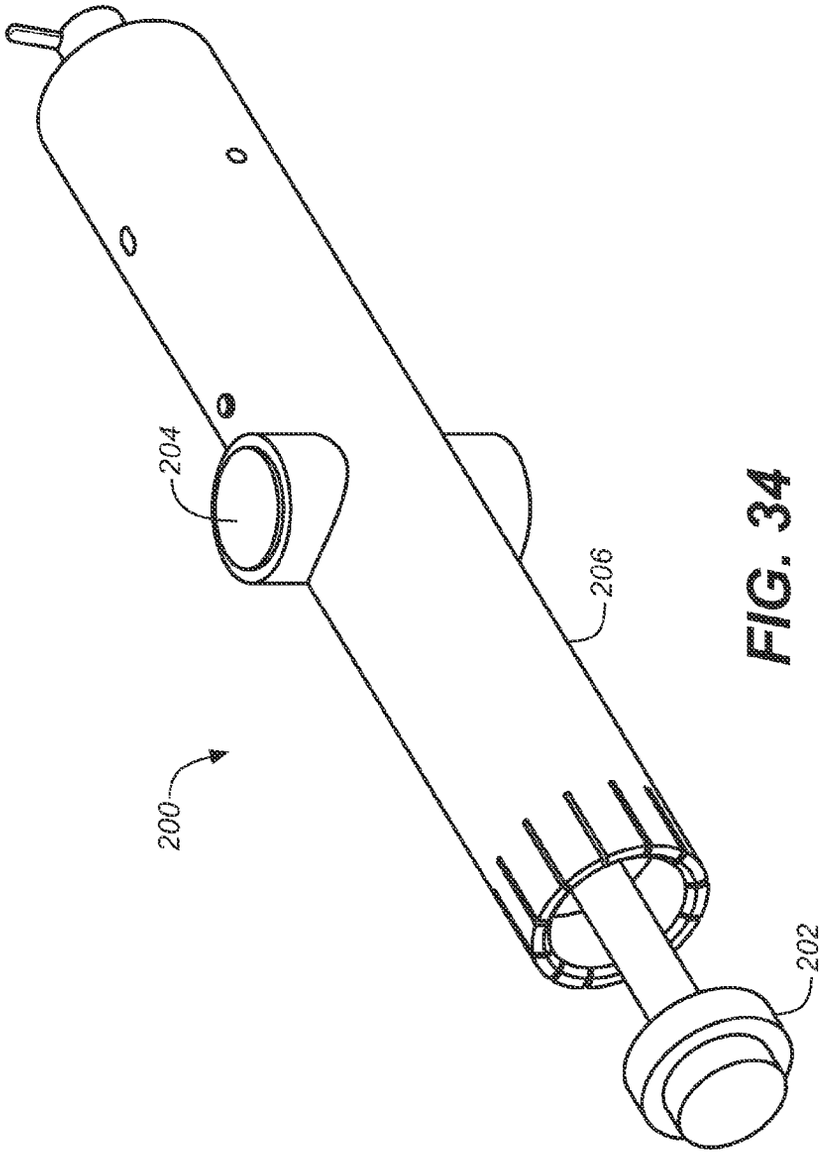



FIG. 34

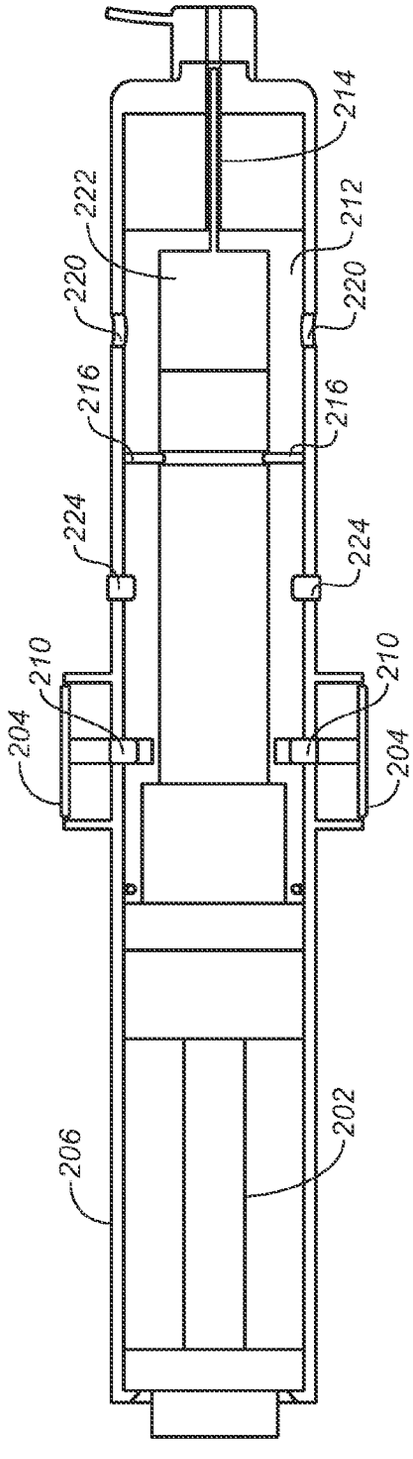



FIG. 35A

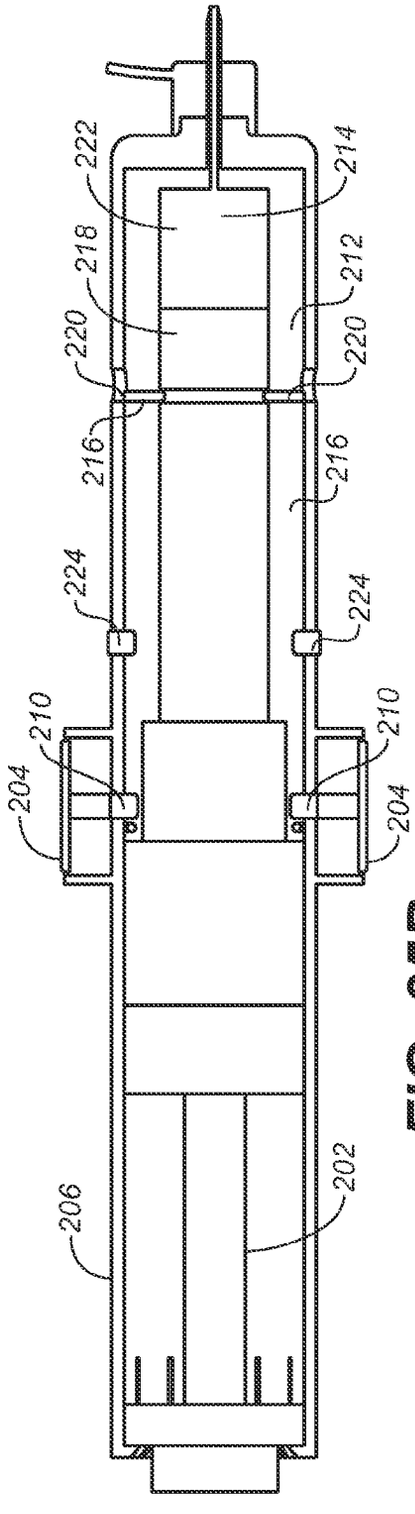



FIG. 35B

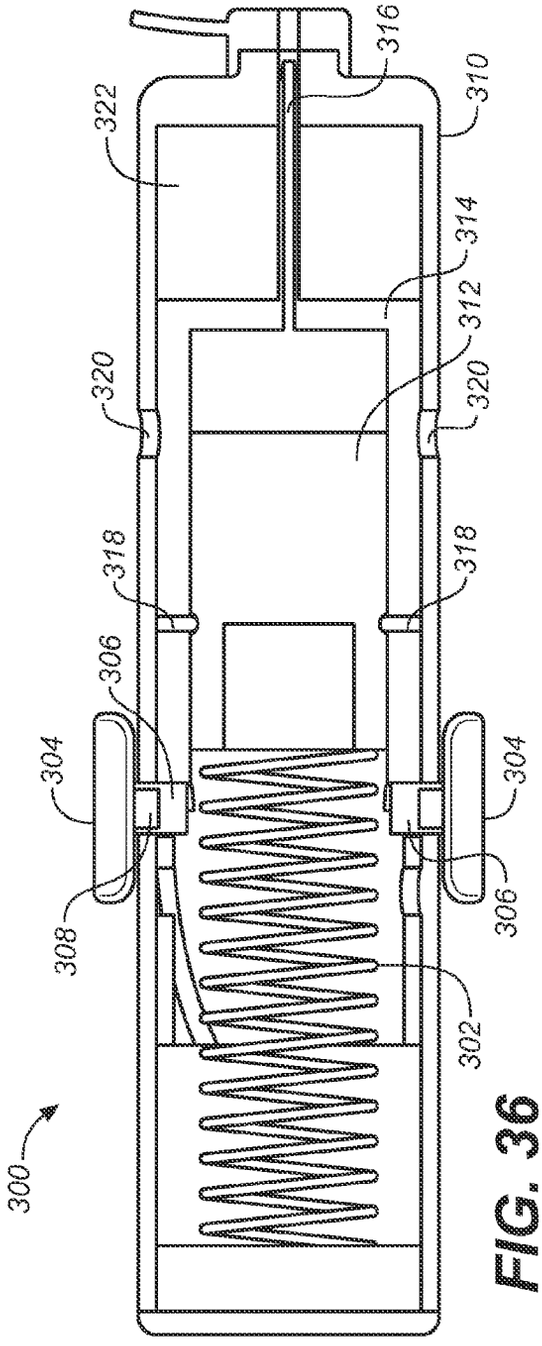



FIG. 36

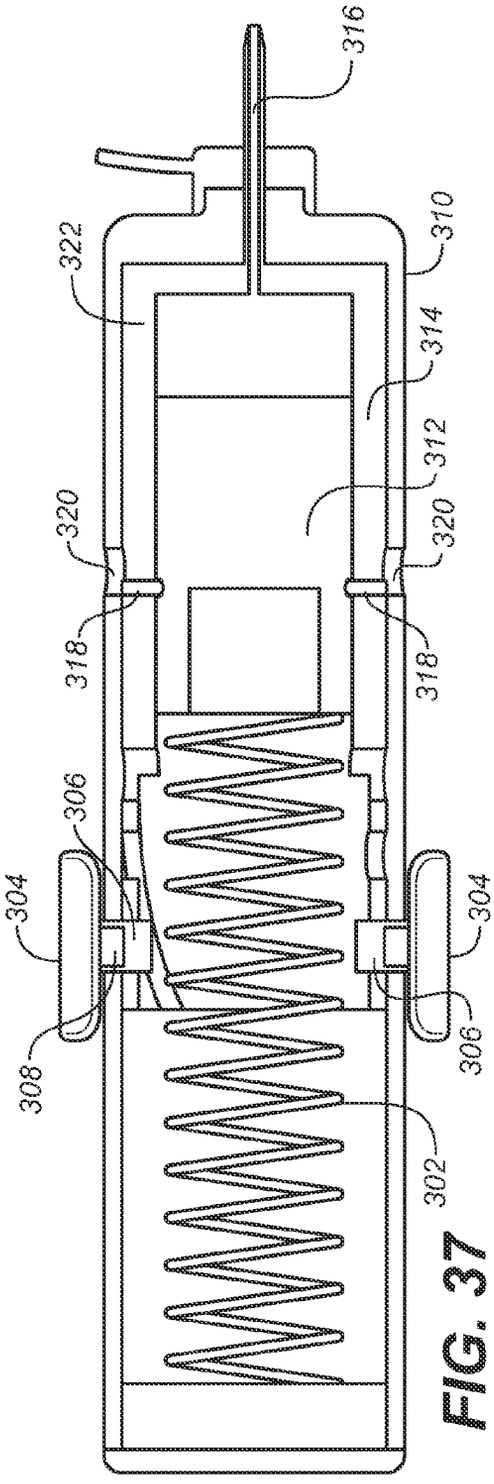



FIG. 37

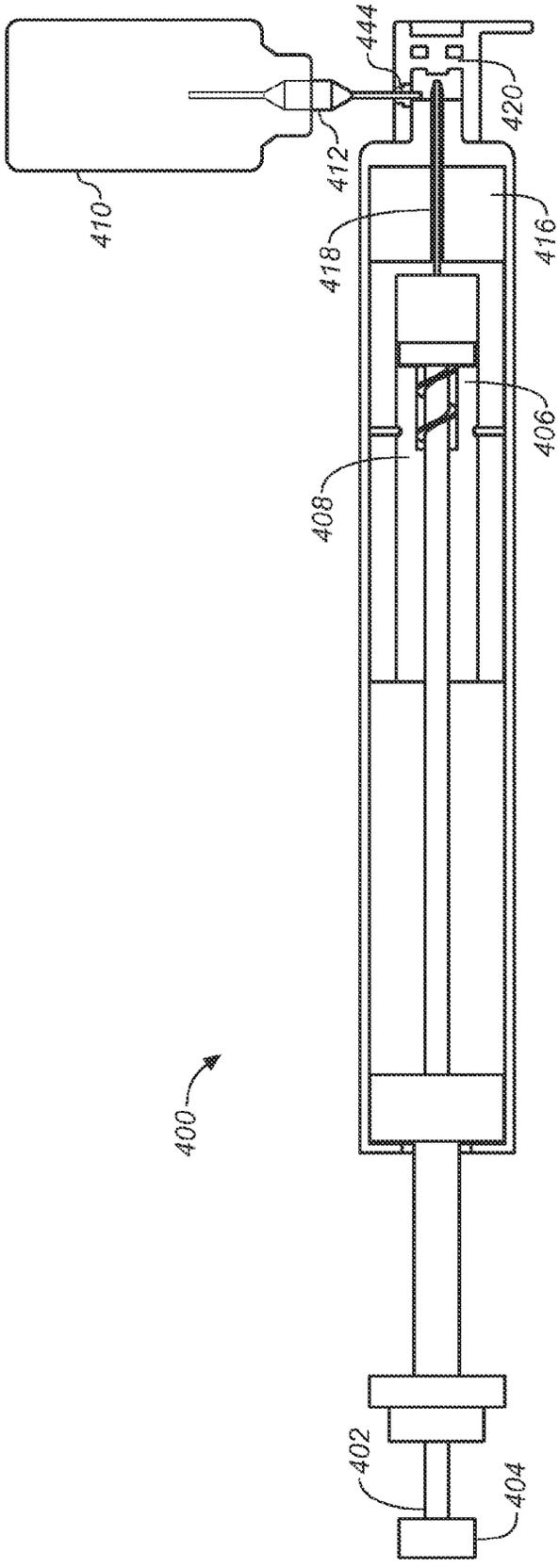



FIG. 38

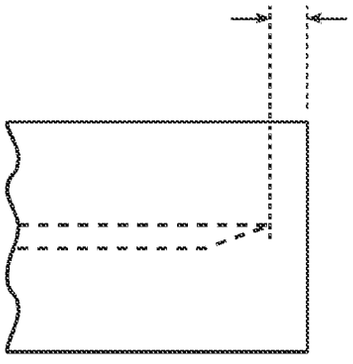


FIG. 39A

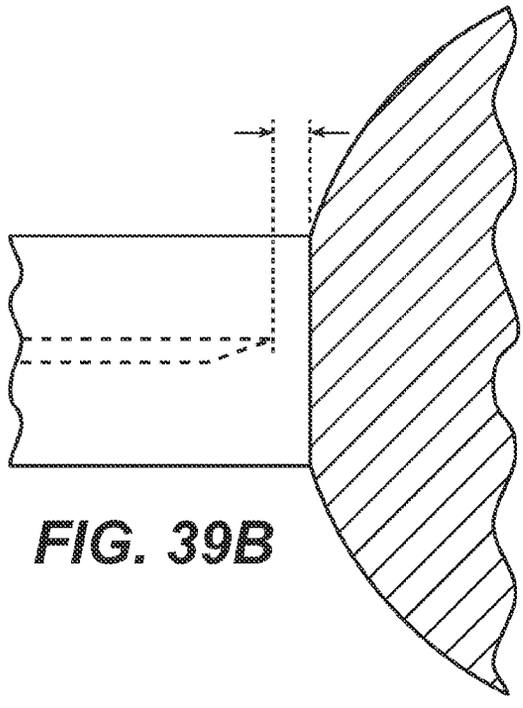


FIG. 39B

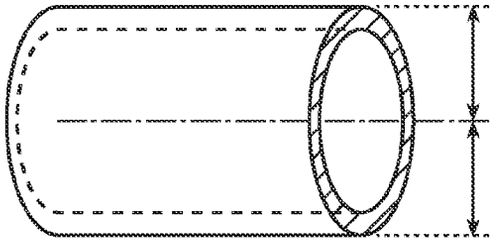


FIG. 39C

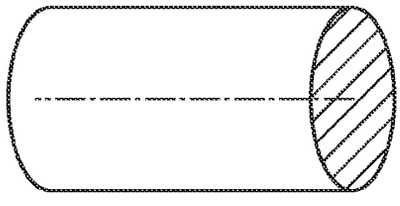


FIG. 39D

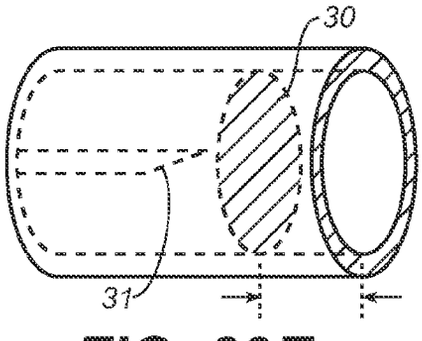



FIG. 39E

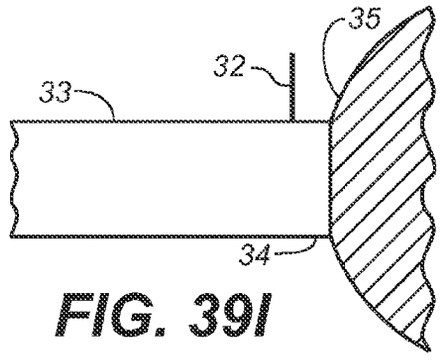



FIG. 39I

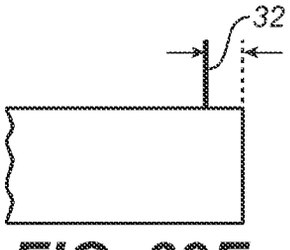



FIG. 39F

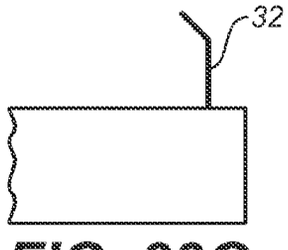



FIG. 39G

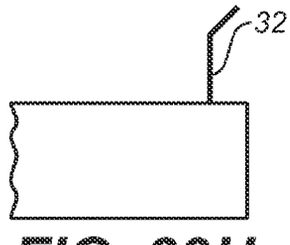



FIG. 39H

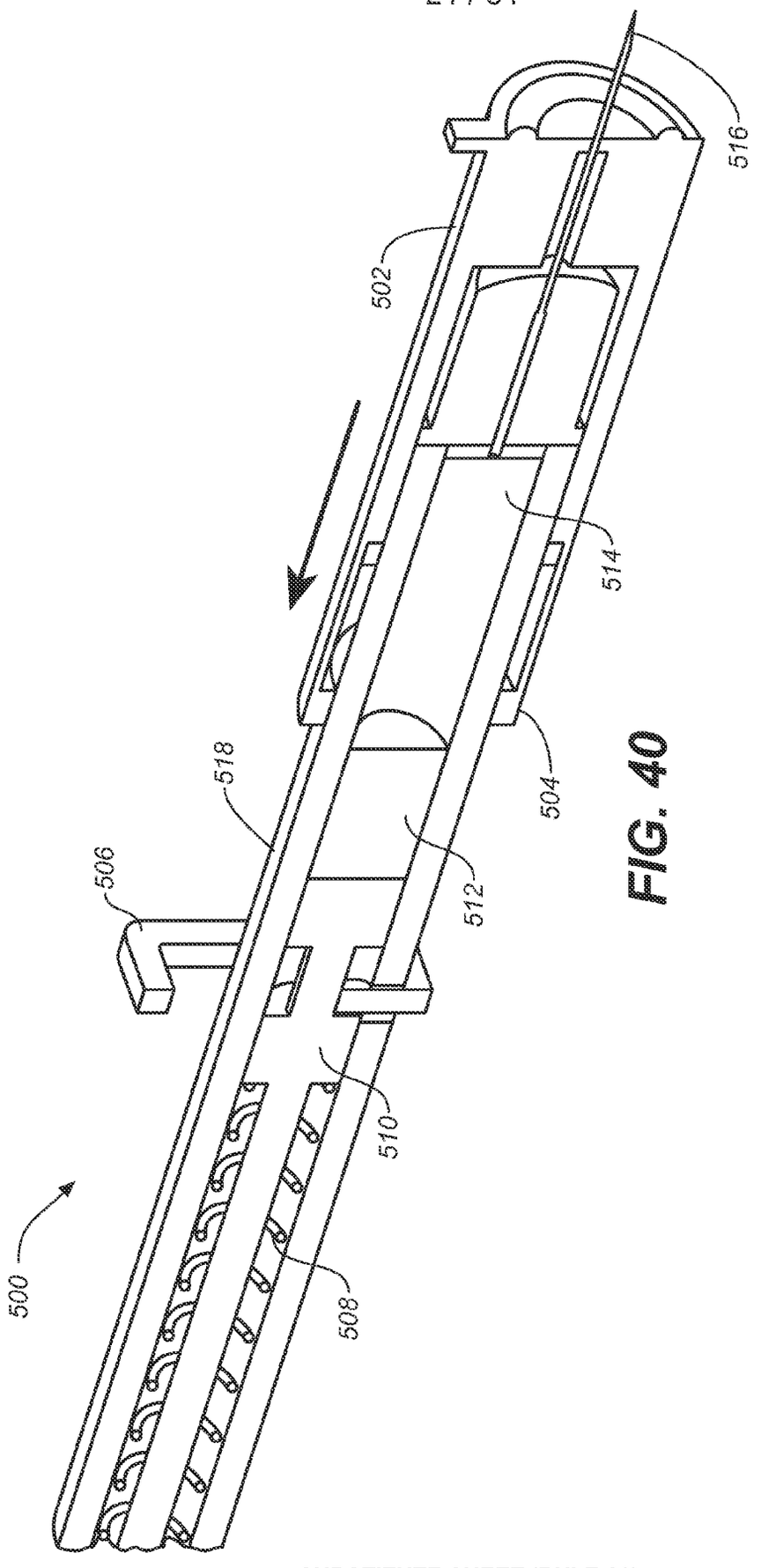



FIG. 40

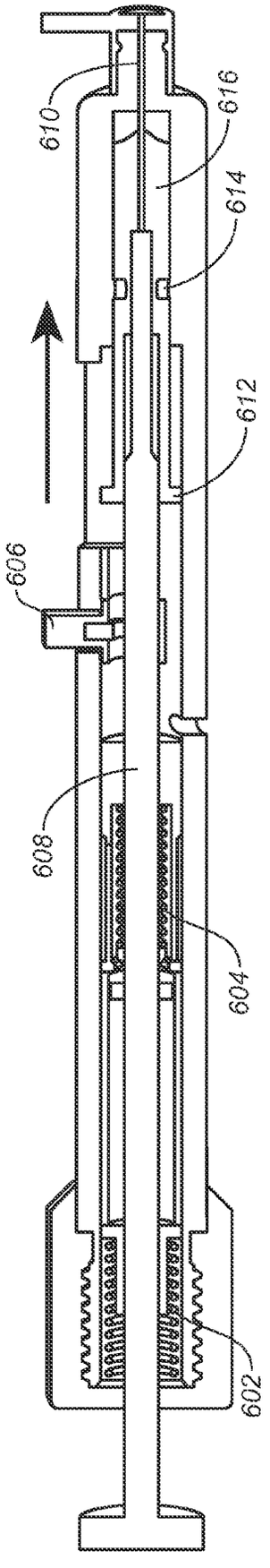



FIG. 41A

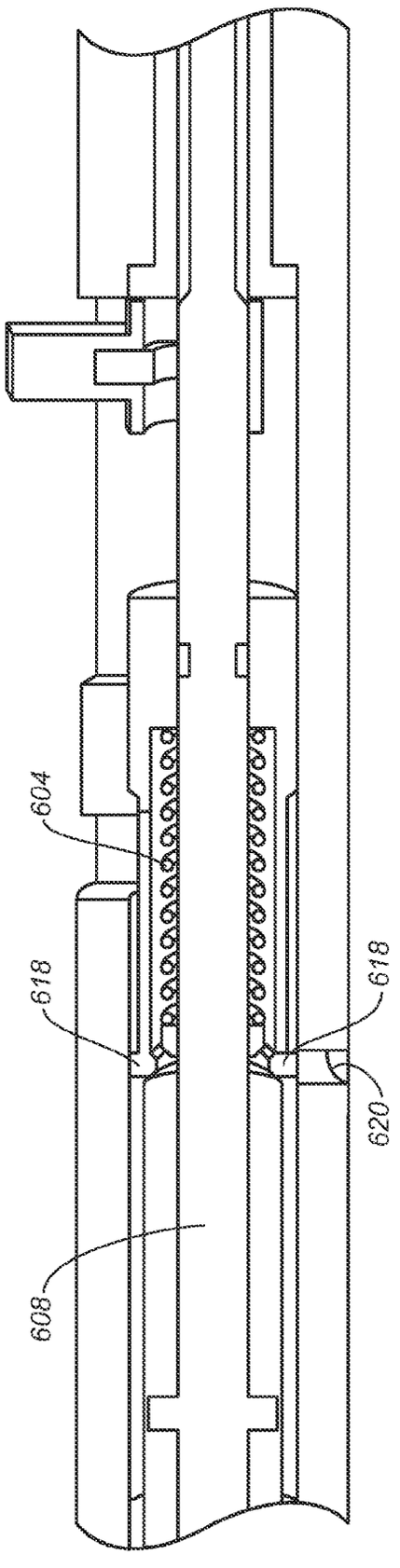



FIG. 41B

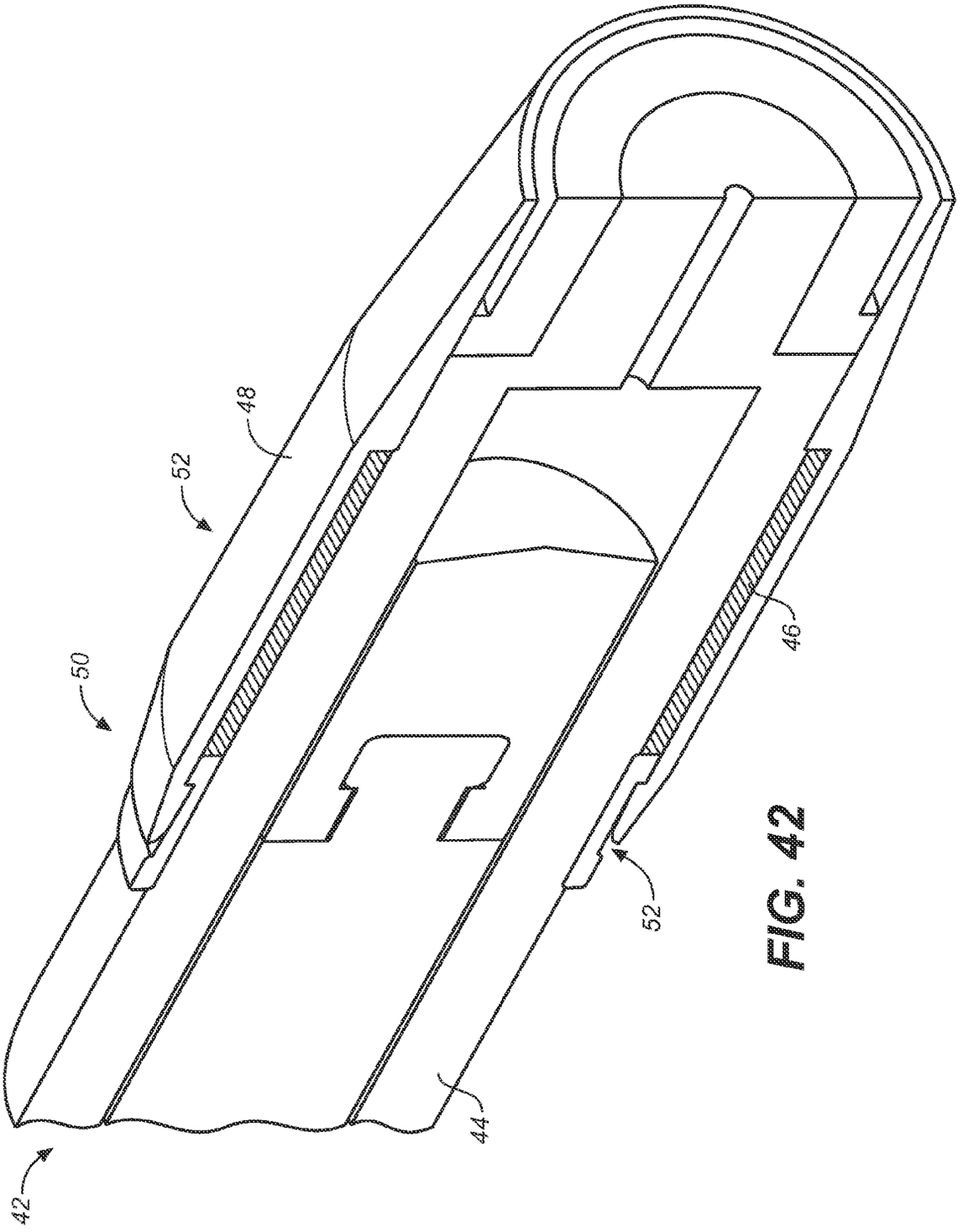



FIG. 42

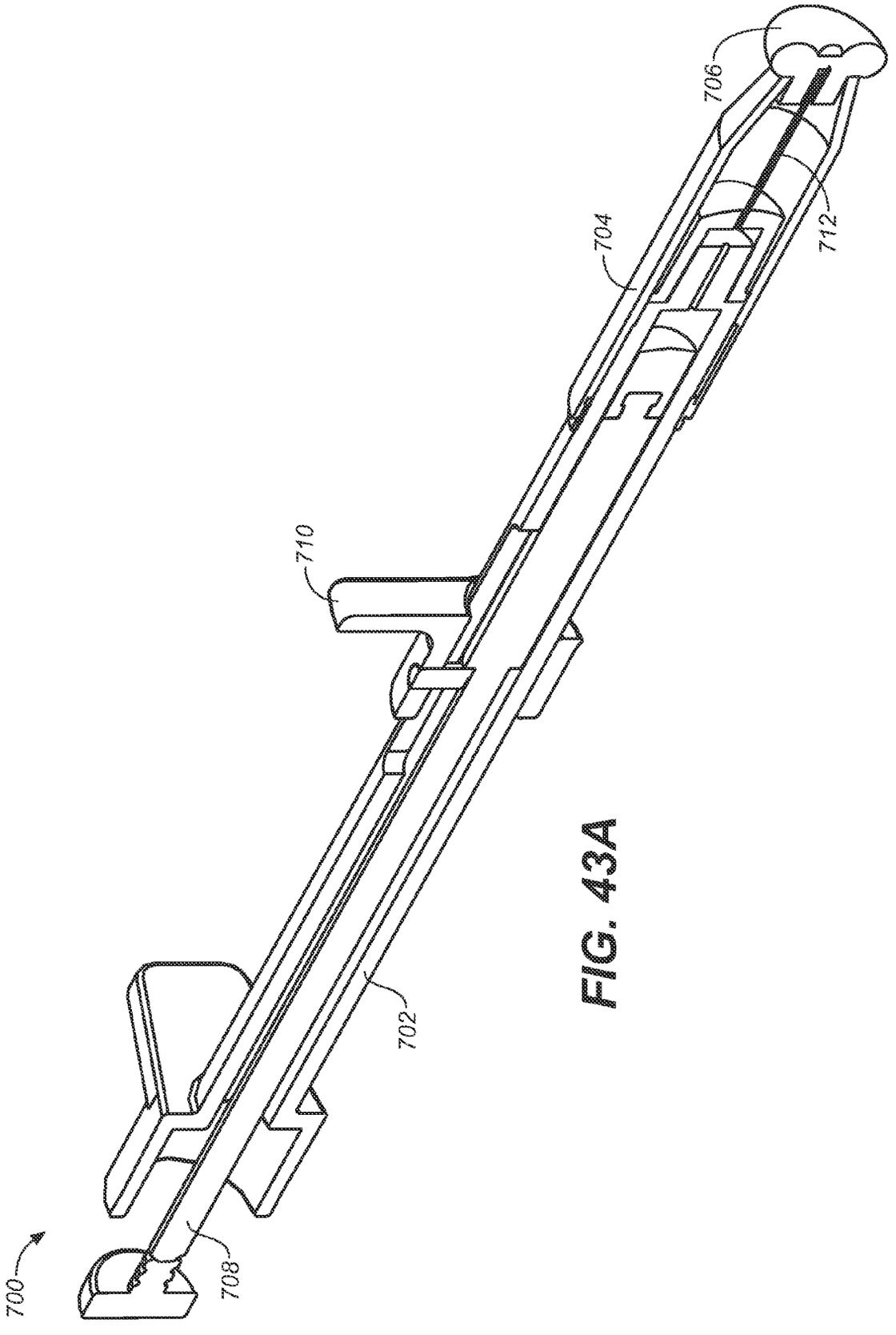



FIG. 43A

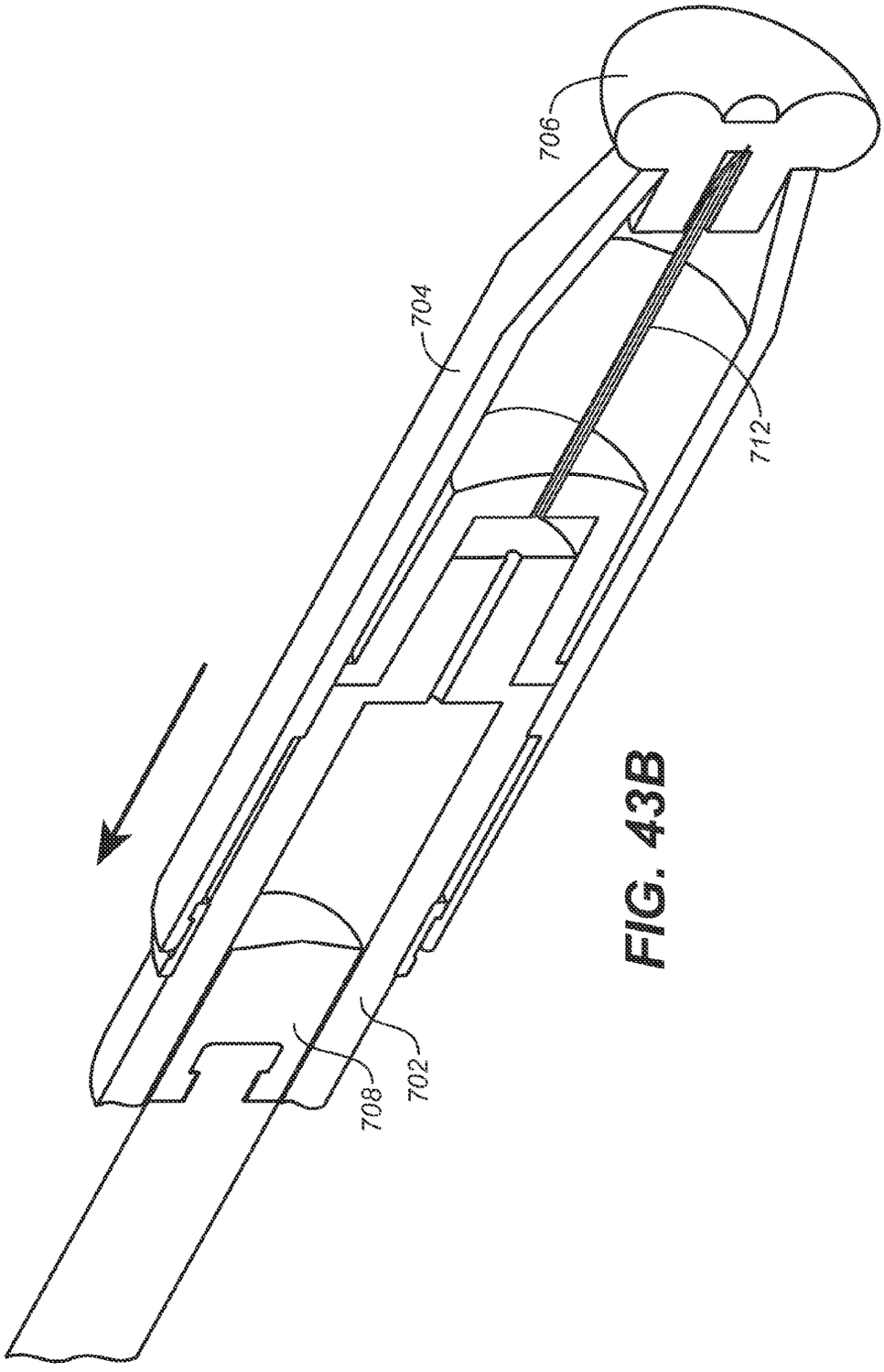



FIG. 43B

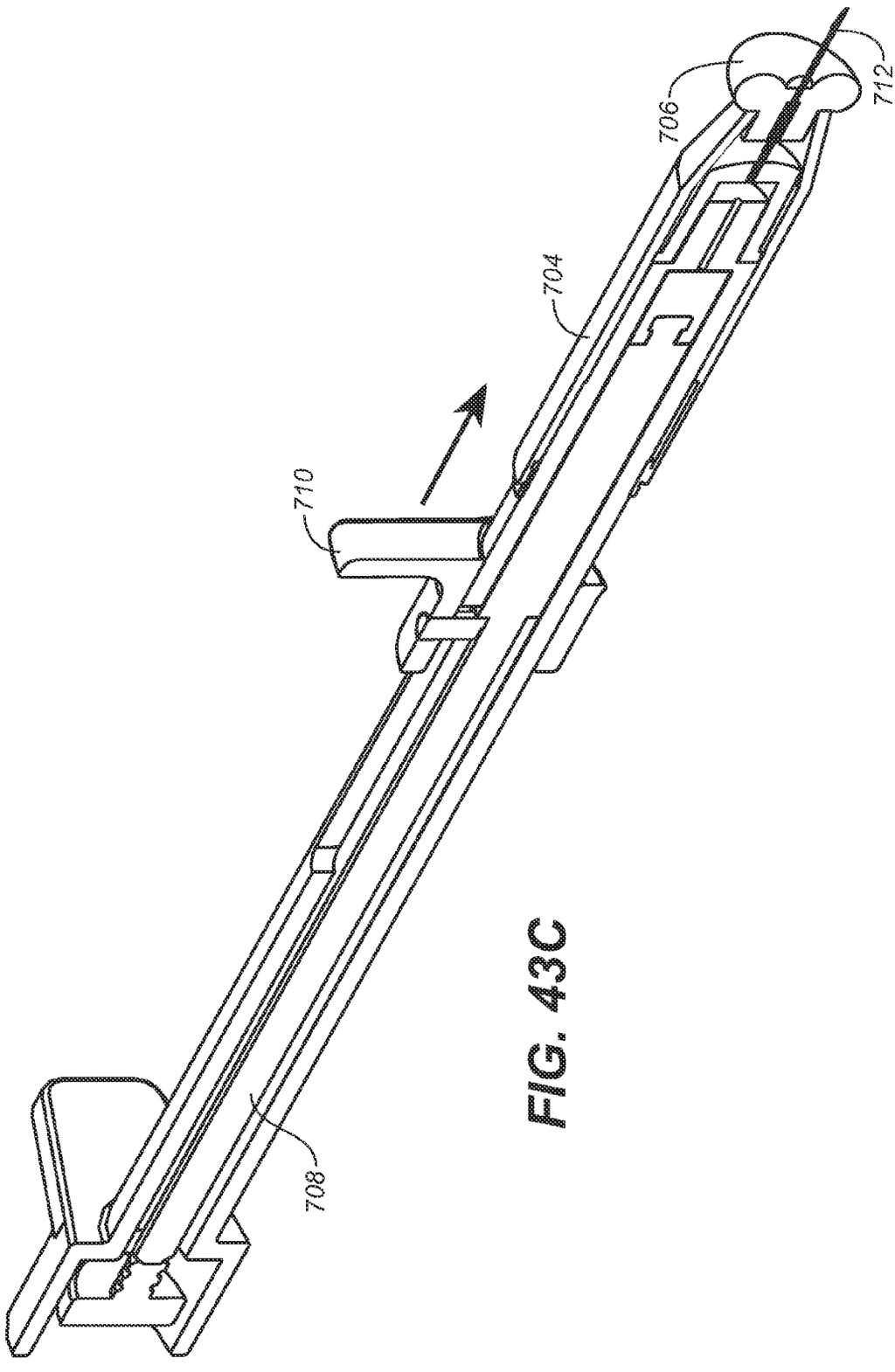



FIG. 43C

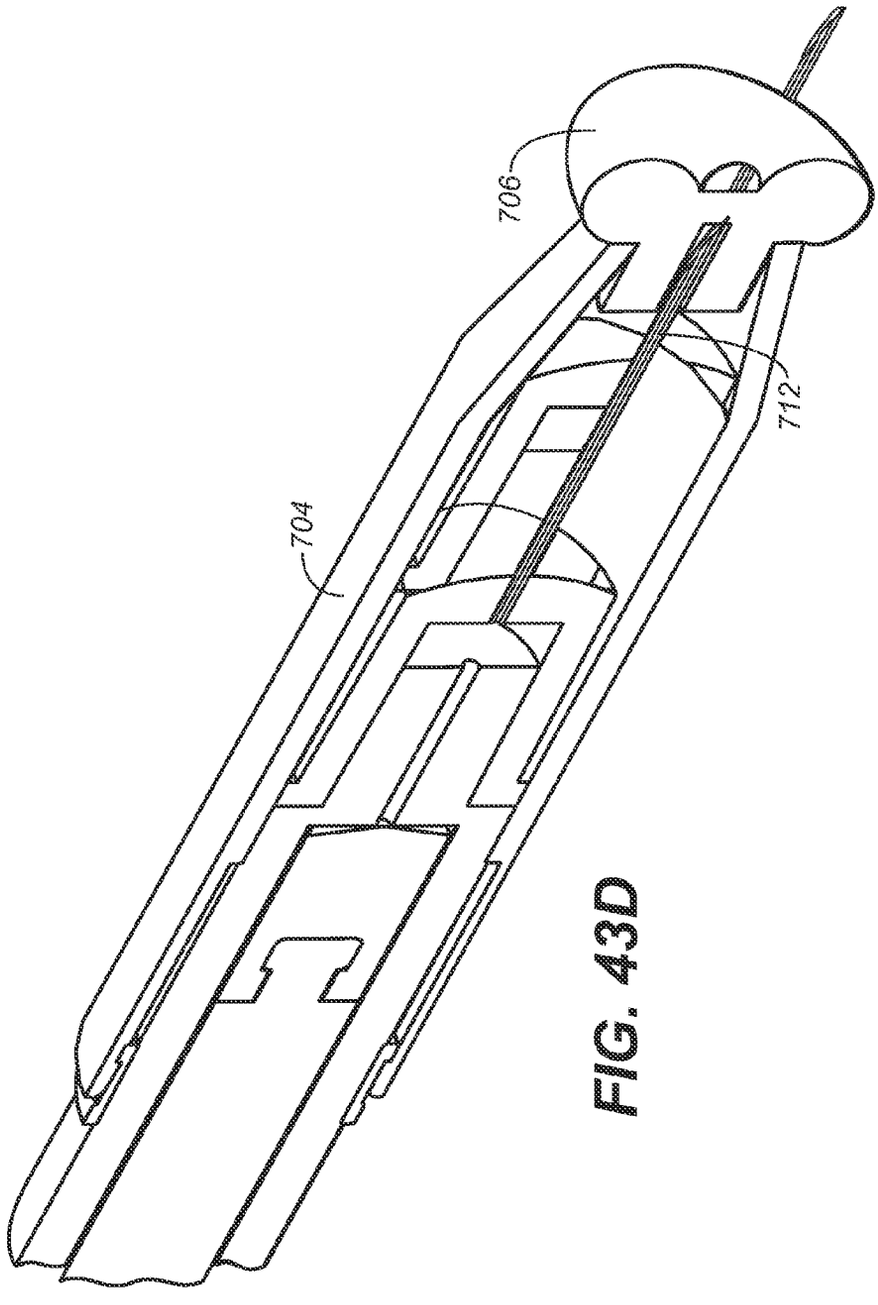



FIG. 43D

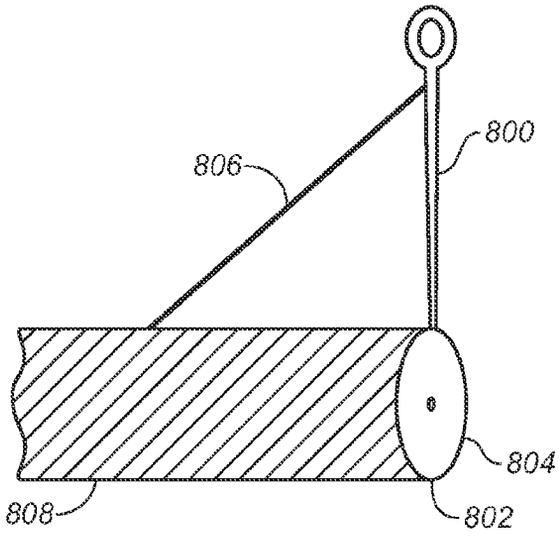



FIG. 44A

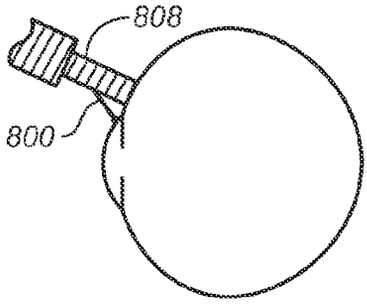



FIG. 44B

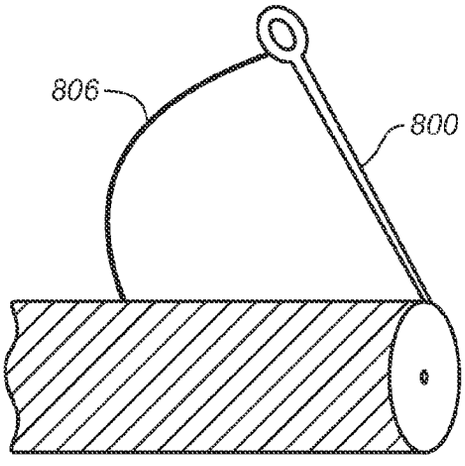



FIG. 44C

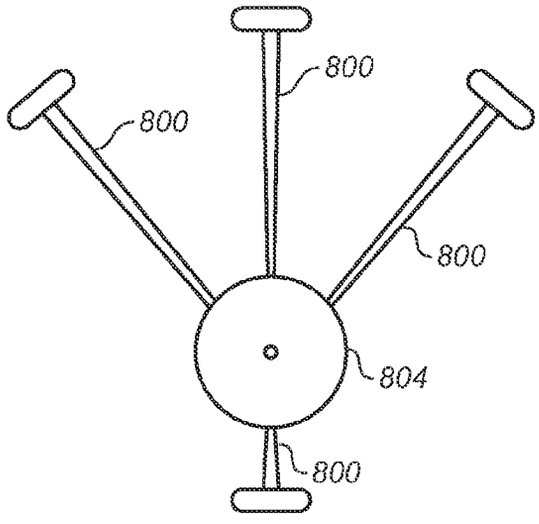



FIG. 44D

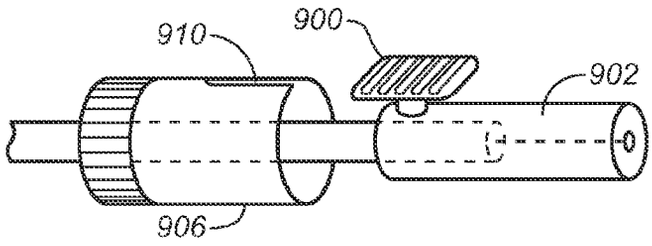



FIG. 45A

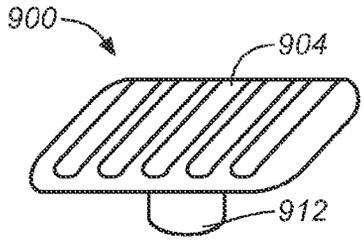



FIG. 45B

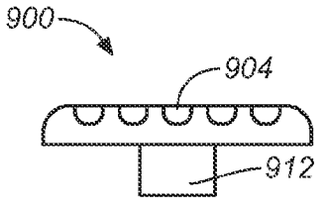



FIG. 45C

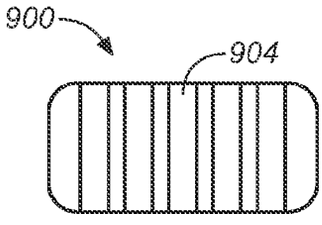
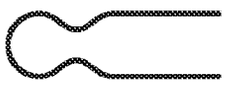



FIG. 45D

FIG. 45E

FIG. 45F

FIG. 45G



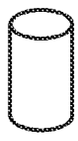


FIG. 45H

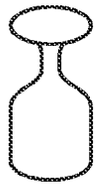


FIG. 45I

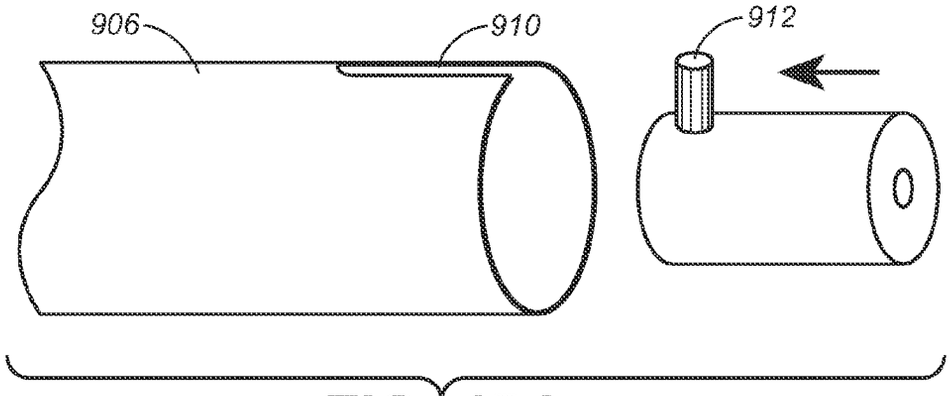



FIG. 45J

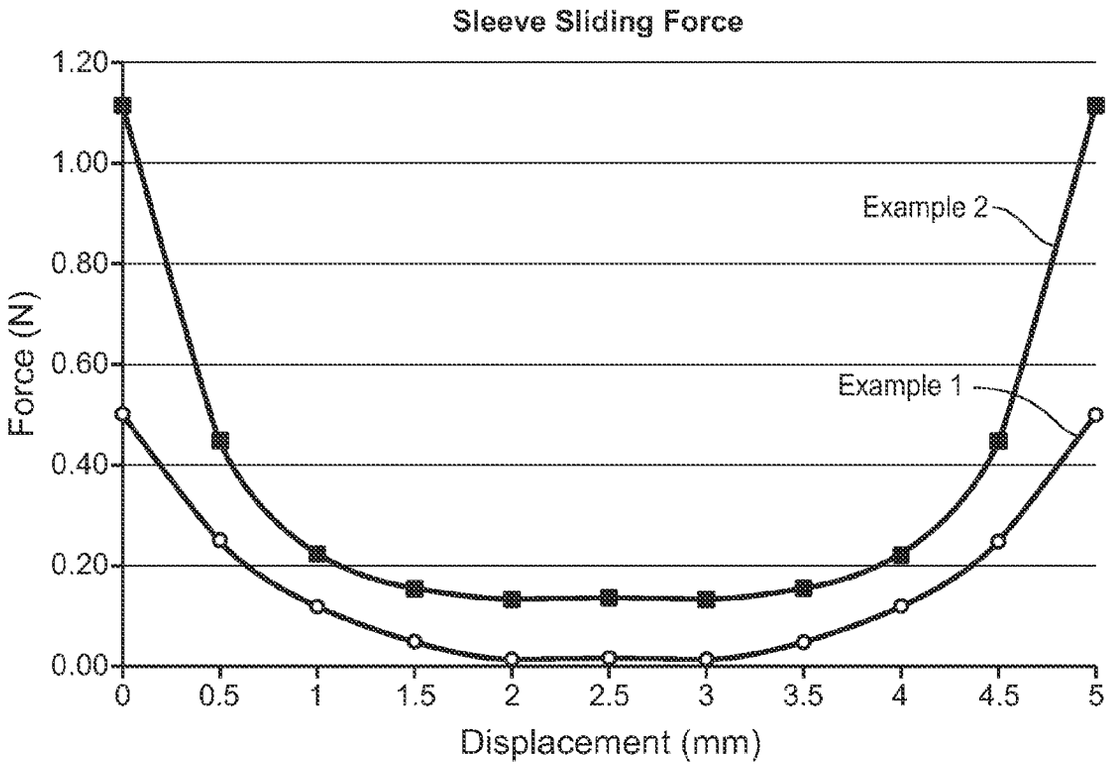



FIG. 46

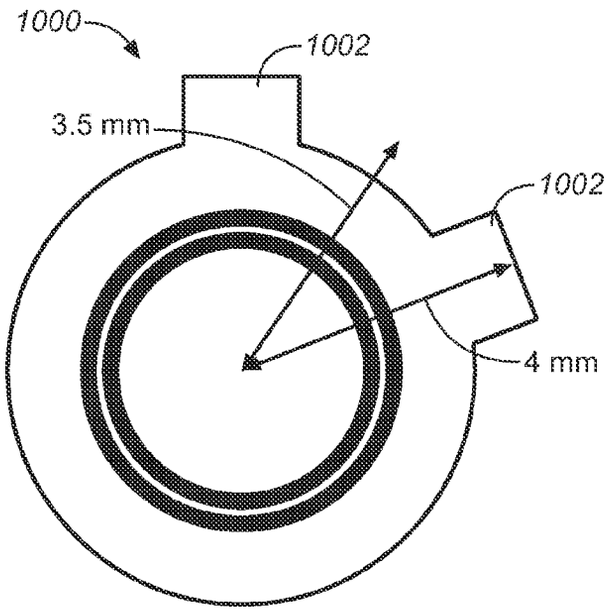



FIG. 47

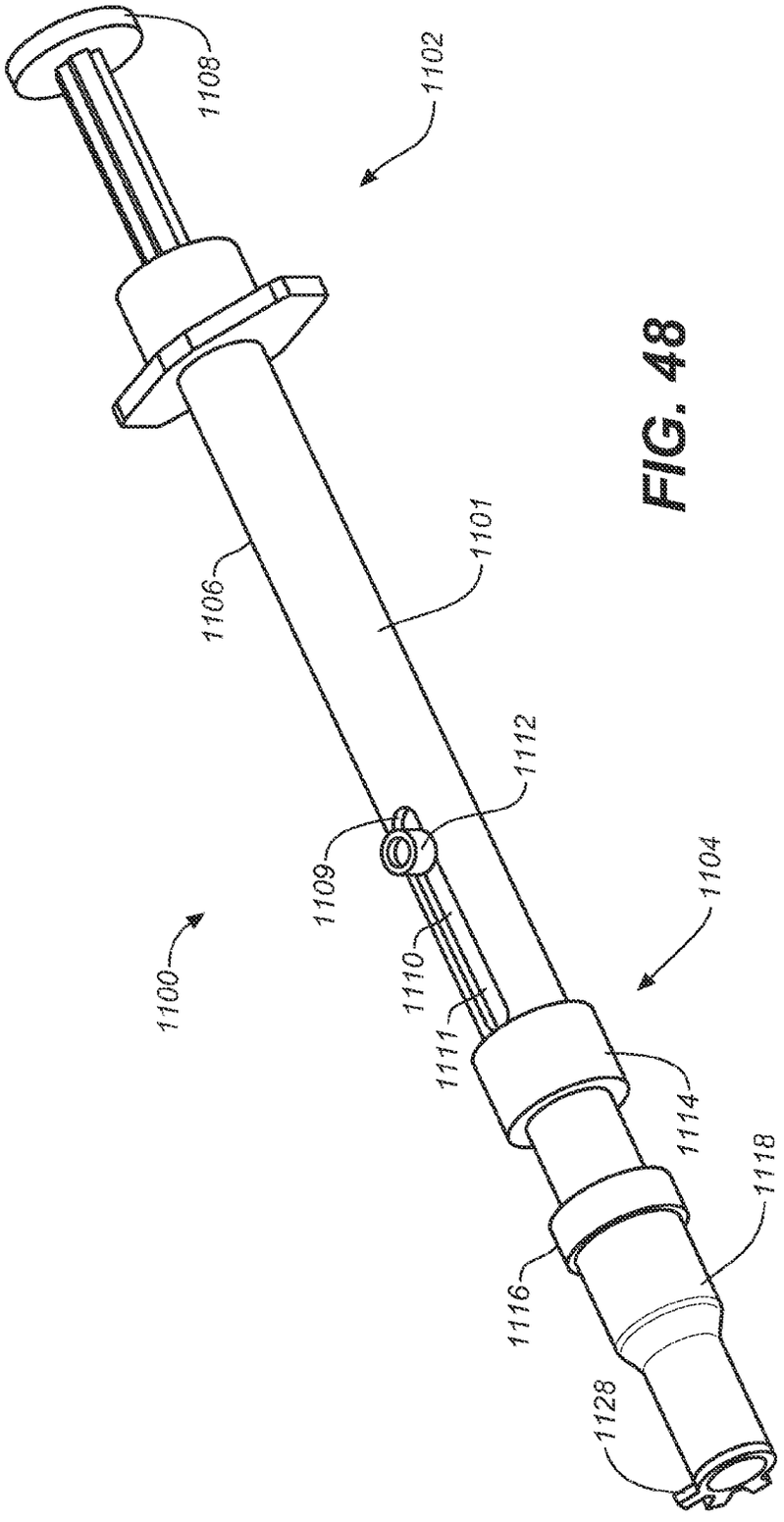



FIG. 48

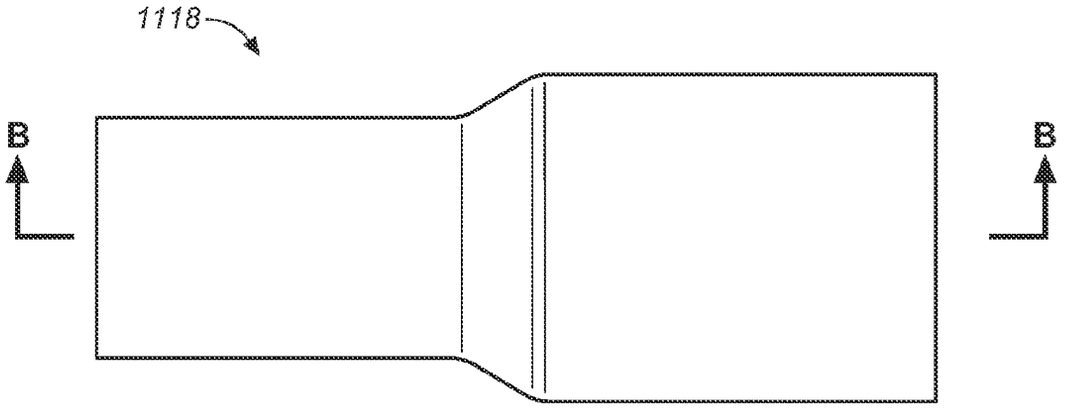



FIG. 49A

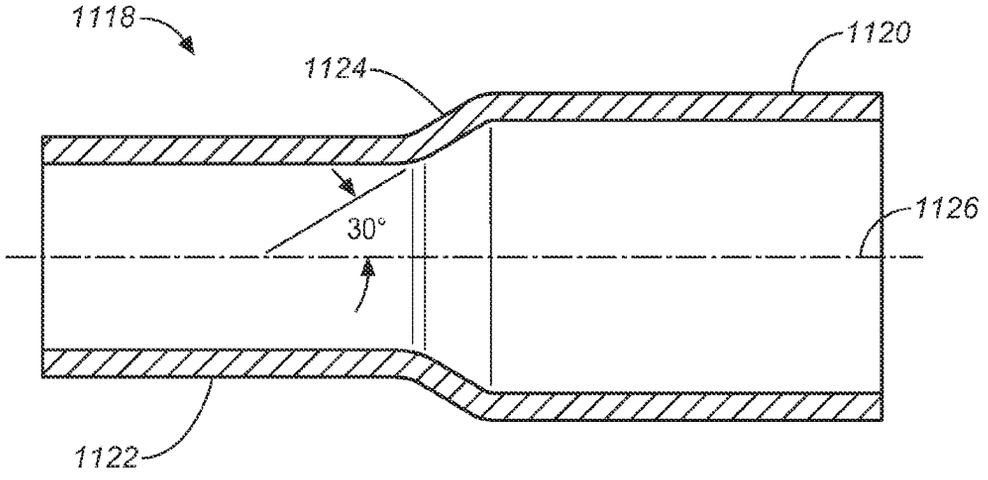



FIG. 49B

FIG. 50

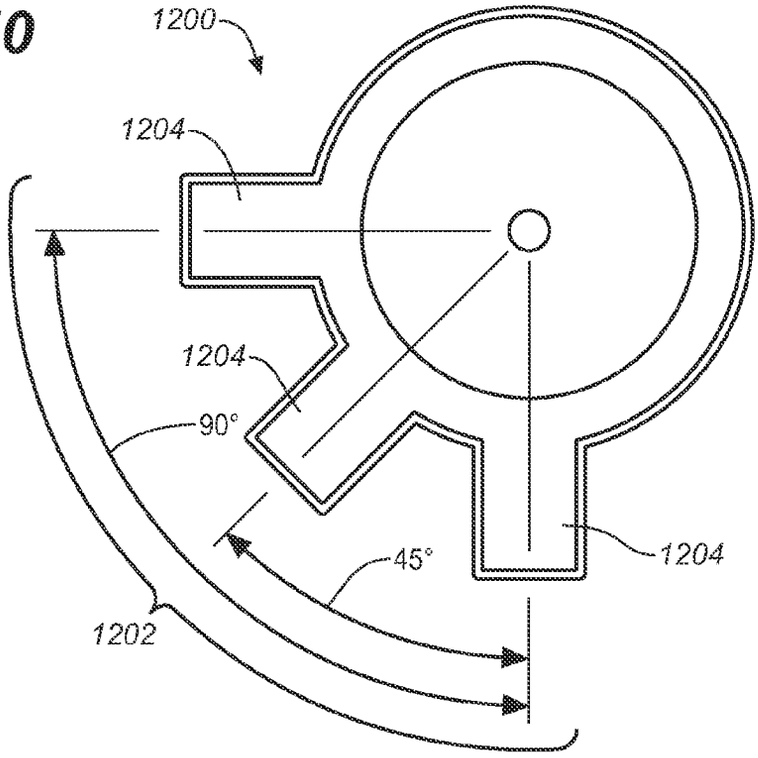
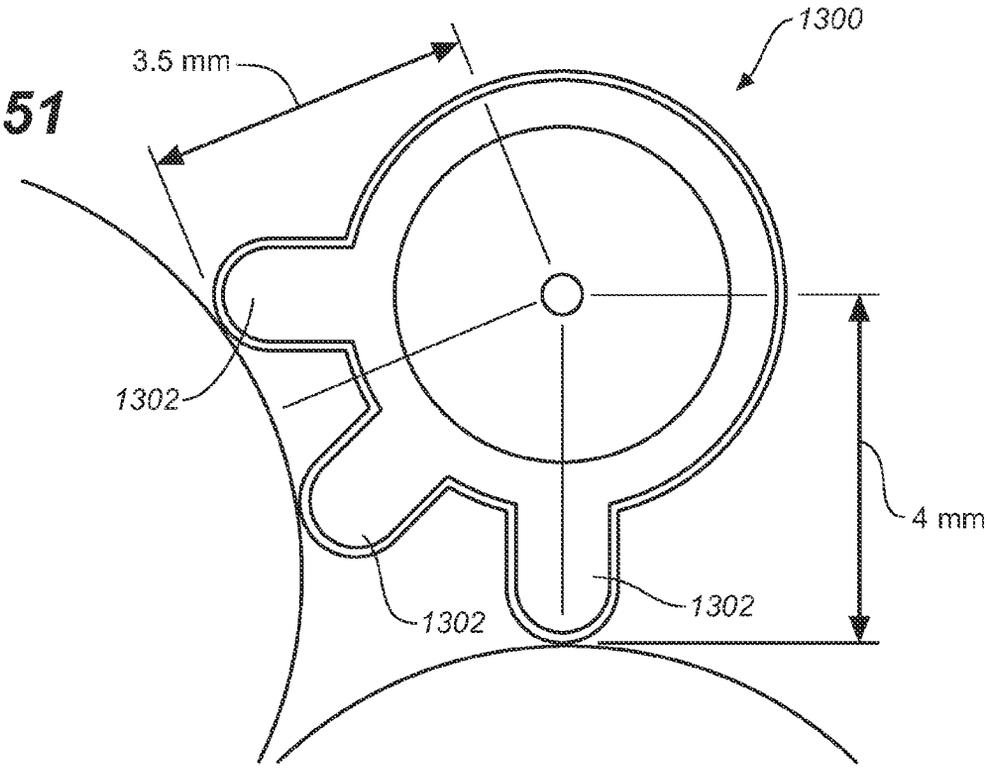



FIG. 51



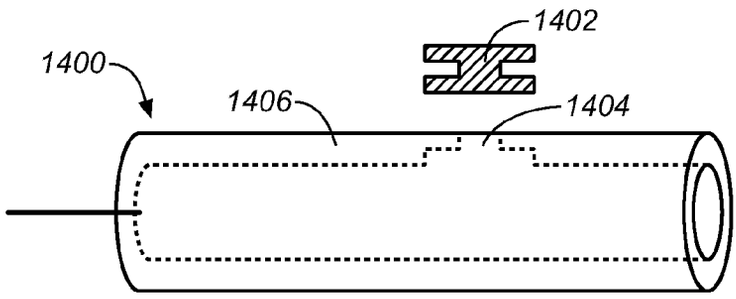



FIG. 52A

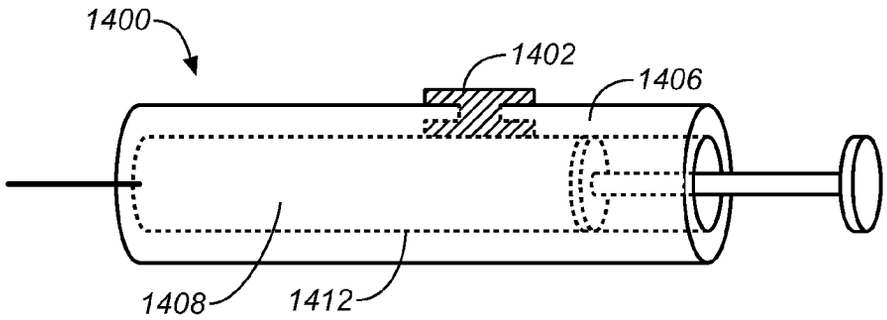



FIG. 52B

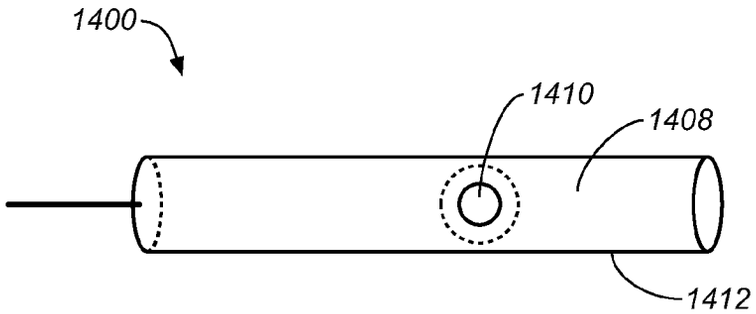



FIG. 52C

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 11/53944

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61M 5/00 (2012.01)
USPC - 604/116
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC: A61M 5/00 (2012.01)
USPC: 604/116

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
IPC: A61M 5/00 (2012.01)
USPC: 424/429, 427; 604/19, 48, 93.01, 110, 116, 173, 181, 187, 190, 192, 199, 218, 294

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (PGPB,USPT,EPAB,JPAB), Google (Patent, Scholar); Keywords: inject$4, eye, intraocular$4, ocular$4, resist$6, bias$4, elastic$4, elastomer$4, band, sheath$4, sleeve, cover$4, needle, cannula, measur$4, locat$4, component, member, template, sector$4, spoke, finger, arm, filter, syringe, barrel, reservoir, ranibizumab, bevacizumab, VEGF, trap,

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | US 2010/0030150 A1 (Paques et al.) 04 February 2010 (04.02.2010) Abstract; para [0051], [0112]-[0115], [0118], [0120]; Fig. 1, 2, 49-54 | 1-23 |
| Y | US 2002/0123721 A1 (Payne et al.) 05 September 2002 (05.09.2002) para [0041], [0042]; Fig. 4 -8 | 1-23 |
| Y | US 6,251,090 B1 (Avery et al.) 26 June 2001 (26.06.2001) col 5, ln 56-64; col 10, ln 61-63; Fig. 6, 18 | 13-23 |
| Y | US 2005/0113806 A1 (De Carvalho et al.) 26 May 2005 (26.05.2005) para [0111], [0124], [0137] | 16, 17, 22, 23 |

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

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 06 February 2012 (06.02.2012) | 15 FEB 2012 |
| Name and mailing address of the ISA/US<br>Mail Stop PCT, Attn: ISA/US, Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-3201 | Authorized officer:<br>Lee W. Young<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

Form PCT/ISA/210 (second sheet) (July 2009)

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 15294906 |
| **Application Number:** | 13750352 |
| **International Application Number:** | |
| **Confirmation Number:** | 5306 |
| **Title of Invention:** | SYRINGE |
| **First Named Inventor/Applicant Name:** | Juergen Sigg |
| **Customer Number:** | 1095 |
| **Filer:** | Andrew K. Holmes/Andrea Jacquin |
| **Filer Authorized By:** | Andrew K. Holmes |
| **Attorney Docket Number:** | PAT055157-US-NP |
| **Receipt Date:** | 19-MAR-2013 |
| **Filing Date:** | 25-JAN-2013 |
| **Time Stamp:** | 11:30:31 |
| **Application Type:** | Utility under 35 USC 111(a) |

## Payment information:

| | |
|---|---|
| Submitted with Payment | no |

## File Listing:

| Document Number | Document Description | File Name | File Size(Bytes)/ Message Digest | Multi Part /.zip | Pages (if appl.) |
|---|---|---|---|---|---|
| 1 | | 55157-US-NP_SuppIDS_2013Mar19.pdf | 777398<br>d35050d412bc15365b784439ab4205c02f03a700 | yes | 3 |

| | Multipart Description/PDF files in .zip description | | |
|---|---|---|---|
| | **Document Description** | **Start** | **End** |
| | Transmittal Letter | 1 | 2 |
| | Information Disclosure Statement (IDS) Form (SB08) | 3 | 3 |

| | | | | | |
|---|---|---|---|---|---|
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 2 | Foreign Reference | WO11123722.pdf | 3827748<br>f78d91cbbb3d030c6655ac2838f80e66a061257e | no | 91 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 3 | Foreign Reference | 16_WO2012149040_.pdf | 2656975<br>e246fe5ae43cf8d93b71d7c5d2169186f804684a | no | 21 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 4 | Foreign Reference | 17_WO2007149334_.pdf | 1901222<br>6c37f0315f475fcf2161f752ce57fd18558faff1 | no | 15 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| 5 | Foreign Reference | 18_WO2012134528_.pdf | 9414286<br>f4d006ca575dd5b1cf4c05c94896b834265eb393 | no | 100 |
| **Warnings:** | | | | | |
| **Information:** | | | | | |
| | | **Total Files Size (in bytes):** | 18577629 | | |

**This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.**

**New Applications Under 35 U.S.C. 111**

**If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.**

**National Stage of an International Application under 35 U.S.C. 371**

**If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.**

**New International Application Filed with the USPTO as a Receiving Office**

**If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.**

Case PAT055157-US-NP

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
Sigg, Juergen et al.
APPLICATION NO: 13/750352
FILED: January 25, 2013
FOR: SYRINGE

Art Unit: 3763
Examiner:

MS: Amendment
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Sir:

This paper is being filed:

☒ supplemental to the Information Disclosure Statements filed January 25, 2013 and January 29, 2013.

☒ within three months of the filing date of the application. Therefore, no fees are required.

☒ before the mailing date of a first Office Action on the merits, and so under 37 C.F.R. §1.97(b)(3) no fees are required.

If a fee is deemed to be required, the Commissioner is hereby authorized to charge such fee to Deposit Account No. 19-0134 in the name of Novartis.

In accordance with 37 C.F.R. §1.56, applicants wish to call the Examiner's attention to the references cited on the attached form(s) PTO/SB/08A/B.

☒ Copies of the non-asterisked references are enclosed herewith.

The Examiner is requested to consider the foregoing information in relation to this application and indicate that each reference was considered by returning a copy of the initialed PTO/SB/08A/B form(s).

Respectfully submitted,

/ Andrew Holmes /

Andrew Holmes
Agent for Applicant
Reg. No. 51,813

Novartis Pharmaceuticals Corporation
One Health Plaza, Bldg. 101
East Hanover, NJ 07936
+1 8627785816

Date: March 19, 2013

CASE PAT055157-US-NP

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10

Express Mail Label Number _____ Date of Deposit _____

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF

Sigg, Juergen et al.

APPLICATION NO: 13/750352

FILED: January 25, 2013

FOR: SYRINGE

Art Unit: 3763

**MS: Missing Parts**
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

RESPONSE TO INFORMATIONAL NOTICE TO APPLICANT

Sir:

In response to the Informational Notice to Applicant mailed February 12, 2013 applicants now submit an original fully executed Oath and Declaration in compliance with 37 CFR 1.63. Please charge the $130 surcharge fee under 37 CFR §1.16(f) to Deposit Account No. 19-0134 in the name of Novartis.

The Commissioner is hereby authorized to charge any additional fees under 37 CFR §1.17 which may be required, or credit any overpayment, to Account No. 19-0134 in the name of Novartis.

Respectfully submitted,

/ Andrew Holmes /

Andrew Holmes
Agent for Applicant
Reg. No. 51,813

Novartis Pharmaceuticals Corporation
One Health Plaza, Bldg. 101
East Hanover, NJ 07936
+1 8627785816

Date: March 27, 2013

PTO/AIA/01 (06-12)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE


# DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

| Title of Invention | SYRINGE |
|---|---|

As the below named inventor, I hereby declare that:

This declaration is directed to:

- ☐ The attached application, or
- ☑ United States application or PCT international application number PCT/EP2013/051491 filed on 25 January 2013

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

## WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Christophe Royer Date (Optional): 08 FEB 2013

Signature: _____

Note: An application data sheet (PTO/AIA/14 or equivalent), including naming the entire inventive entity, must accompany this form. Use an additional PTO/SB/AIA/01 form for each additional inventor.

PTO/AIA/01 (09-12)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE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|---|---|

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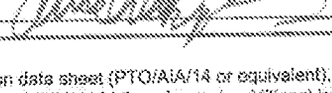
LEGAL NAME OF INVENTOR

Inventor: Andrew Mark Bryant Date (Optional): 5th February 2013

Signature: 

Note: An application data sheet (PTO/AIA/14 or equivalent), including naming the entire inventive entity, must accompany this form. Use an additional PTO/SB/AIA/01 form for each additional inventor.

PTO/AIA/01 (06-12)
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# DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention: SYRINGE

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This declaration is directed to:

- ☐ The attached application, or
- ☑ United States application or PCT international application number PCT/EP2013/051491 filed on 25 January 2013.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

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LEGAL NAME OF INVENTOR

Inventor: Heinrich Martin Buettgen Date (Optional): 8. 10 2013

Signature: H. Buettgen

Note: An application data sheet (PTO/AIA/14 or equivalent), including naming the entire inventive entity, must accompany this form. Use an additional PTO/SB/AIA/01 form for each additional inventor.

PTO/AIA/01 (06-12)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE


# DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

| Title of Invention | SYRINGE |
|---|---|

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- ☐ The attached application, or
- ☑ United States application or PCT international application number PCT/EP2013/051491 filed on 25 January 2013

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

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LEGAL NAME OF INVENTOR

Inventor: Marie Picci Date (Optional): 08/6/2013

Signature: [signature]

Note: An application data sheet (PTO/AIA/14 or equivalent), including naming the entire inventive entity, must accompany this form. Use an additional PTO/SB/AIA01 form for each additional inventor.

PTO/AIA/01 (06-12)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE


# DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

| Title of Invention | SYRINGE |
|---|---|

As the below named inventor, I hereby declare that:

This declaration is directed to:

- ☐ The attached application, or
- ☑ United States application or PCT international application number PCT/EP2013/051491 filed on 25 January 2013.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

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## WARNING:

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LEGAL NAME OF INVENTOR

Inventor: Juergen Sigg Date (Optional): 8.2.2013

Signature:

Note: An application data sheet (PTO/AIA/14 or equivalent), including naming the entire inventive entity, must accompany this form. Use an additional PTO/SB/AIA/01 form for each additional inventor.

# Electronic Patent Application Fee Transmittal

| | |
|---|---|
| **Application Number:** | 13750352 |
| **Filing Date:** | 25-Jan-2013 |
| **Title of Invention:** | SYRINGE |
| **First Named Inventor/Applicant Name:** | Juergen Sigg |
| **Filer:** | Andrew K. Holmes/Andrea Jacquin |
| **Attorney Docket Number:** | PAT055157-US-NP |

Filed as Large Entity

## Utility under 35 USC 111(a) Filing Fees

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Basic Filing:** | | | | |
| **Pages:** | | | | |
| **Claims:** | | | | |
| **Miscellaneous-Filing:** | | | | |
| Late Filing Fee for Oath or Declaration | 1051 | 1 | 140 | 140 |
| **Petition:** | | | | |
| **Patent-Appeals-and-Interference:** | | | | |
| **Post-Allowance-and-Post-Issuance:** | | | | |
| **Extension-of-Time:** | | | | |

| Description | Fee Code | Quantity | Amount | Sub-Total in USD($) |
|---|---|---|---|---|
| **Miscellaneous:** | | | | |
| | | | **Total in USD ($)** | **140** |

# Electronic Acknowledgement Receipt

| | |
|---|---|
| **EFS ID:** | 15366100 |
| **Application Number:** | 13750352 |
| **International Application Number:** | |
| **Confirmation Number:** | 5306 |
| **Title of Invention:** | SYRINGE |
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| | 2 | 2006128564 | WO | A1 | 2006-12-07 | BAXTER INT | | ☐ |
| | 3 | 2006047325 | WO | A1 | 2006-05-04 | SHAMS NAVEED | | ☐ |
| | 4 | 201578690 | CN | U | 2010-09-15 | JIANYOU WANG | English Abstract | ☐ |
| | 5 | 2371406 | EP | | 2011-10-05 | Taisei Kako Co., LTD | equivalent of WO2010/064667 | ☐ |
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(54) Title: INJECTABLE COMBINATION THERAPY FOR EYE DISORDERS

(57) Abstract: The present invention provides composition, methods, and articles of manufacture for treating an eye disorder, e.g., a disorder characterized by macular degeneration, choroidal neovascularization, or retinal neovascularization. One method of the invention comprises the step of: administering first and second therapeutic agents to the subject's eye in a single procedure, wherein the first therapeutic agent provides rapid improvement in the condition of the subject's eye and the second therapeutic agent is administered as a sustained release formulation of the second therapeutic agent. For example, the first and second therapeutic agents are administered by intravitreal injection. The first therapeutic agent may be dissolved in a liquid medium located in the syringe and the sustained formulation of the second therapeutic agent may comprise an ocular implant or plurality of particles located in the needle. The therapeutic agents may be selected from the group consisting of angiogenesis inhibors and complement inhibitors.

# INJECTABLE COMBINATION THERAPY FOR EYE DISORDERS

## Cross-Reference to Related Applications

[0001] This application claims priority to, and the benefit of, U.S. Provisional Patent Application No. 60/760,974, filed Jan. 19, 2006, and U.S.S.N. 11/544,389, filed Oct. 6, 2006, both of which are incorporated herein by reference.

## Background of the Invention

[0002] Macular degeneration is a term that refers to and describes a number of different diseases characterized by degenerative changes in the macula, all of which lead to a loss of central vision. The macula is a small area in the retina of the eye, approximately 3 to 5 millimeters in size, adjacent to the optic nerve. It is the most sensitive area of the retina and contains the fovea, a depressed region that allows for high visual acuity and contains a dense concentration of cones, the photoreceptors that are responsible for color vision. Age-related macular degeneration (ARMD) is the most common cause of functional blindness in developed countries for those over 50 years of age. The disease is characterized by progressive degeneration of the retina, retinal pigment epithelium (RPE), and underlying choroid (the highly vascular tissue that lies beneath the RPE, between the retina and the sclera). Cells in the RPE recycle visual pigment (rhodopsin), phagocytose photoreceptor tips daily as part of rod and cone regeneration, and transport fluid across the membrane to the choroid. Central vision deteriorates when cells in the RPE cease to function properly. Despite extensive investigation, the pathogenesis of ARMD is not fully understood. Oxidative stress, inflammation, genetic background, and environmental or behavioral factors such as smoking and diet may contribute.

[0003] A clinical hallmark of ARMD is the appearance of drusen, localized deposits of lipoproteinaceous material that accumulate in the space between the RPE and Bruch's membrane. Drusen are typically the earliest clinical finding in ARMD, and the existence, location, and number of drusen are used in classifying the disease into stages and monitoring progression (Ambati, J., et al., *Surv. Ophthalmol.*, 48(3): 257-293, 2003; "Preferred Practice Pattern: Age-Related Macular Degeneration", American Academy of Ophthalmology, 2003).

[0004] ARMD has been classified into "dry" and "wet" (exudative, or neovascular) forms. Dry ARMD is much more common than wet, but the dry form can progress to the wet form, and the two occur simultaneously in a significant number of cases. Dry ARMD is typically characterized by progressive apoptosis of cells in the RPE, overlying photoreceptor cells, and frequently also the underlying cells in the choroidal capillary layer. Confluent areas (e.g., at

least 175 μm in minimum diameter) of RPE cell death accompanied by overlying photoreceptor atrophy are referred to as geographic atrophy. Patients with this form experience a slow and progressive deterioration in central vision. Wet ARMD is characterized by bleeding and/or leakage of fluid from abnormal vessels that have grown from the choroidal vessels (choriocapillaris) beneath the RPE and macula. This can be responsible for sudden and disabling vision loss. Much of the vision loss that patients experience is due to such choroidal neovascularization (CNV) and its complications. A subtype of neovascular ARMD in which angiomatous proliferation originates from the retina and extends posteriorly into the subretinal space, eventually communicating in some cases with choroidal new vessels has been identified (Yannuzzi, L.A., et al., *Retina*, 21(5):416-34, 2001). This form of neovascular ARMD, termed retinal angiomatous proliferation (RAP) can be particularly severe. The existence of macular drusen is a strong risk factor for development of both wet and dry forms of ARMD.

**[0005]** The panels of Figure 1 show structures present in a normal eye and some of the processes that occur in ARMD. Figures 1A and 1B show structures present in the anterior and posterior segments of the eye. Figures 1C-1E depict the outer layers of a normal eye (1C), an eye suffering from dry ARMD (1D), and an eye suffering from wet ARMD (1E). The outer nuclear layer (ONL) contains nuclei of rod and cone photoreceptors. Each photoreceptor contains an inner segment (IS) and outer segment (OS), the latter of which contains the pigment rhodopsin, which initiates the phototransduction cascade following exposure to light. The RPE lies below the photoreceptors and above Bruch's membrane. As shown in Figures 1D and 1E, the normal structure of the retina is disrupted in a variety of ways as in patients with ARMD.

**[0006]** Macular edema is associated with a variety of eye disorders including ARMD, diabetic retinopathy, inflammatory conditions such as anterior or posterior uveitis, etc. The macula becomes thickened as a result of the accumulation of fluid that leaks from weakened or otherwise abnormal blood vessels into nearby tissues. Leakage of blood or other fluids and the resulting increase in macular thickness can lead to acute alterations in visual acuity, color perception, etc. Thus macular edema can contribute to the visual disturbances and loss experienced by individuals suffering from ARMD and a variety of other eye disorders.

**[0007]** Development of pharmacological therapies for ARMD and other ocular disorders associated with neovascularization in the eye is an area of active investigation. Much effort has focused on methods for destroying or sealing abnormal blood vessels and/or inhibiting their development. Photodynamic therapy involves systemic intravenous administration of a light-sensitive dye (verteporfin) which is activated in the eye by a laser, resulting in formation of toxic products within the abnormal blood vessels. Local administration of angiogenesis inhibitors to

the eye shows considerable promise. Pegaptanib sodium (Macugen®; Pfizer/Eyetech) was approved by the U.S. Food and Drug Administration for treatment of wet age-related macular degeneration in late 2004. Macugen is an aptamer that binds to an isoform of vascular endothelial growth factor (VEGF), a protein that acts as a signal in triggering the abnormal blood vessel growth, increased permeability, and consequent leakage that characterize wet ARMD. Binding of Macugen to VEGF prevents it from binding to VEGF receptors, thereby inhibiting its activity. Other angiogenesis inhibitors for the treatment of exudative ARMD include monoclonal antibodies such as ranibizumab (Lucentis®; Genentech) that bind to VEGF and block its interaction with VEGF receptors.

**[0008]** Angiogenesis inhibitors that interfere with signal transduction pathways that play a fundamental role in angiogenesis, such as the VEGF pathway, offer a powerful approach to controlling neovascularization. However, therapy with angiogenesis inhibitors alone has a number of disadvantages. Clinical trials of angiogenesis inhibitors that interfere with the VEGF pathway have involved their administration in solution by intravitreal injection at intervals of 4-6 weeks. Unfortunately this procedure is associated with a significant risk of complications such as traumatic lens injury, retinal detachment, and endophalmitis associated with either trauma or intraocular infection. With an overall risk of 1%, over the course of a year a dosing interval of 6 weeks would result in an overall risk of about 9% per eye, while a dosing interval of 4 weeks would result in an overall risk of about 13% per eye. For these and other reasons, current approaches to the use of angiogenesis inhibitors remain a less than optimal solution to treating wet ARMD. There remains a need in the art for improved approaches to treating ARMD. There also remains a need for improved approaches to treating other conditions characterized by macular degeneration, choroidal neovascularization, retinal neovascularization, retinal angiomatous proliferation, and/or blood vessel leakage in the eye.

## Summary of the Invention

**[0009]** The present invention provides compositions, methods, and articles of manufacture for the treatment of eye disorders, particularly those associated with macular degeneration, CNV, and/or retinal neovascularization (RNV). In one aspect, the invention provides a method of treating an eye disorder characterized by macular degeneration, CNV, or RNV, the method comprising the step of: administering first and second therapeutic agents to the subject's eye in a single procedure, wherein the first therapeutic agent provides rapid improvement in the condition of the subject's eye and the second therapeutic agent is administered as a sustained

release formulation of the second therapeutic agent. In certain embodiments of the invention the second therapeutic agent is a long-acting therapeutic agent. In certain embodiments of the invention at least a portion of the first therapeutic agent, optionally essentially the entire administered dose of the first therapeutic agent, is provided as a component of a sustained release formulation. The first and second therapeutic agents may be provided as components of a single sustained release formulation or as components of separate sustained release formulations.

**[0010]** In certain embodiments of the invention the procedure is an injection procedure, e.g., an intravitreal injection. In certain embodiments the procedure is an injection procedure in which, prior to administration, the first therapeutic agent is contained in a syringe and the sustained release formulation comprising the second therapeutic agent is contained in a needle attached to the syringe. For example, the first therapeutic agent may be dissolved in a liquid medium located in the syringe and the sustained formulation of the second therapeutic agent may comprise an ocular implant located in the needle.

**[0011]** In another aspect, the invention provides a method of treating an eye disorder characterized by macular degeneration, CNV, or RNV comprising the step of: administering first and second compositions to a subject's eye in a single procedure, wherein the first composition comprises a first therapeutic agent that provides rapid improvement in the condition of the subject's eye and the second composition comprises a second therapeutic agent that is administered as a sustained release formulation comprising the second therapeutic agent. Either or both of the compositions can contain a plurality of therapeutic agents, e.g., two or more angiogenesis inhibitors, two or more complement inhibitors, or an angiogenesis inhibitor and a complement inhibitor.

**[0012]** In another aspect the invention provides a method of administering first and second therapeutic agents to the eye of a subject comprising: injecting (i) a solution containing the first therapeutic agent and (ii) a solid ocular implant containing the second therapeutic agent into the subject's eye in a single injection procedure.

**[0013]** In any embodiment of the invention, either or both therapeutic agents may be an angiogenesis inhibitor or a complement inhibitor. In any embodiment of the invention the sustained release formulation may comprise an ocular implant. In any embodiment of the invention the sustained release formulation may comprise a polymer and one or more therapeutic agents.

**[0014]** In other aspects, the invention provides articles of manufacture. The invention provides an article of manufacture comprising (i) a first therapeutic agent effective for treating

an eye disorder; and (ii) a needle containing a second therapeutic agent. The article of manufacture may further comprise a syringe. The syringe may contain a therapeutic agent.

**[0015]** In anyembodiment of the present invention, the eye disorder can be a macular degeneration related condition, diabetic retinopathy, retinopathy of prematurity, or any condition featuring CNV, RNV, or RAP.

**[0016]** In any embodiment of the invention that features a complement inhibitor, the complement inhibitor can be any complement inhibitor known in the art, e.g., a viral complement control protein (VCCP) or fragment or variant thereof, a peptide or peptide analog that binds to a complement component, an antagonist of a complement receptor. The VCCP can be a poxvirus VCCP (PVCCP) or a herpesvirus VCCP (HVCCP). The PVCCP can be from vaccinia virus, variola virus, etc. The peptide or peptide analog can be, e.g., compstatin or a derivative thereof.

**[0017]** In any embodiment of the invention that features an angiogenesis inhibitor, the angiogenesis inhibitor may be any angiogenesis inhibitor known in the art. The angiogenesis inhibitor may be selected from the group consisting of: Macugen® (pegaptanib sodium) or another VEGF aptamer or nucleic acid ligand; Lucentis® (ranibizumab), Avastin® (bevacizumb) or another antibody or antibody fragment that specifically binds to VEGF; combretastatin or a derivative or prodrug thereof such as Combretastatin A4 Prodrug (CA4P); VEGF-Trap; EVIZON™ (squalamine lactate); AG-013958 (Pfizer, Inc.); JSM6427 (Jerini AG), β2-glycoprotein 1 (β2-GP1), and a short interfering RNA (siRNA) or short hairpin RNA (shRNA) that inhibits expression of one or more VEGF isoforms, inhibits expression of a VEGF receptor, or inhibits expression of any other molecule whose expression in the eye contributes to angiogenesis. In certain embodiments of the invention the therapeutic agent is not a steroid.

**[0018]** Those of skill in the art will appreciate that certain compounds encompassed by the structures herein may exhibit tautomerism, conformational isomerism, geometric isomerism and/or stereoisomerism. It should be understood that the invention encompasses use of any tautomeric, conformational isomeric, enantiomeric and/or geometric isomeric forms of the compounds described herein. Any references herein employing nomenclature that corresponds to illustrated structural formulae that represent only one of several tautomeric forms (or resonance structures) are not intended to limit the scope of the compounds described herein. Those of skill in the art also will recognize that the compounds disclosed as of use in the invention may exist in many different protonation states, depending on, among other things, the pH of their environment. Where structural formulae provided herein depict the compounds in only one of several possible protonation states, it will be understood that these structures are

illustrative only, and that the invention is not limited to any particular protonation state--any and all protonated forms are intended to fall within the scope of the invention.

**[0019]** Compounds of use in this invention may, in certain embodiments, bear multiple positive or negative charges and may have appropriate counter ions associated therewith. The identity of the associated counter ions are may be governed by the synthesis and/or isolation methods by which the compounds are obtained. Counter ions include, but are not limited to, chloride and other halides, acetate, trifluoroacetate, citrate, sulfate, phosphate, etc., and mixtures thereof. It will be understood that the identity of any associated counter ion is not a critical feature and that the invention encompasses the compounds in association with any type of counter ion. Moreover, as the compounds can exists in a variety of different forms, the invention is intended to encompass not only forms that are in association with counter ions (e.g., dry salts), but also forms that are not in association with counter ions (e.g., aqueous or organic solutions).

**[0020]** Unless otherwise stated or otherwise clearly evident from the context, the invention makes use of standard methods of molecular biology, cell culture, animal maintenance, ophthalmologic examination, and administration of therapeutic agents to subjects, etc., and uses art-accepted meanings of terms. This application refers to various patents and publications. The contents of all articles, books, patents, patent applications, and other publications mentioned in this application are incorporated herein by reference. In addition, the following publications are incorporated herein by reference: *Current Protocols in Molecular Biology*, *Current Protocols in Immunology*, *Current Protocols in Protein Science*, and *Current Protocols in Cell Biology*, all John Wiley & Sons, N.Y., edition as of July 2002; Sambrook, Russell, and Sambrook, *Molecular Cloning: A Laboratory Manual*, 3rd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, 2001; *Kuby Immunology*, 4th ed., Goldsby, R.A., Kindt, T.J., and Osborne, B. (eds.), W.H. Freeman, 2000, *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 10th Ed. .McGraw Hill, 2001, Katzung, B. (ed.) *Basic and Clinical Pharmacology*, McGraw-Hill/Appleton & Lange; 9th edition (December 2003), *Ophthalmic Surgery: Principles and Practice*, 3rd ed., W.B. Saunders Company, 2002; Albert, DM and Lucarelli, MJ (eds.), *Clinical Atlas of Procedures in Ophthalmic Surgery*, American Medical Association, 2003. In the event of a conflict or inconsistency between any of the incorporated references and the instant specification, the specification shall control, it being understood that the determination of whether a conflict or inconsistency exists is within the discretion of the inventors and can be made at any time.

**Brief Description of the Drawing**

**[0021]** ***Figures 1A-1E*** show schematic representations of the anterior and posterior segments of the eye (1A and 1B) and the outer layers of the eye (1C-1E). Figure 1C depicts a normal eye. Figure 1D depicts an eye suffering from dry ARMD. Figure 1E depicts an eye suffering from exudative ARMD. ONL = outer nuclear layer; IS = inner segment; OS = outer segment; RPE = retinal pigment epithelial layer; BM = Bruch's membrane; CC = choriocapillaris. From Tezel, T., et al., *Trends in Molecular Medicine*, 10(9), 417-420, 2004.

**[0022]** ***Figure 2*** shows a consensus sequence for a short consensus repeat (SCR), a module found in complement control proteins. From Smith, SA, et al., *J. Virol.* 74(12), 5659-5666, 2000.

**[0023]** ***Figures 3A and 3B*** show sequences of vaccinia virus complement control protein precursor (SEQ ID NO: 33) and the mature vaccinia virus complement control protein (SEQ ID NO: 34).

**[0024]** ***Figure 4*** shows a sequence comparison of mature complement control proteins from a variety of orthopoxvirus isolates (SEQ ID NO: 35 – 42). The corresponding genetic loci are listed. Modified from Smith, SA, et al., *J. Virol.* 74(12), 5659-5666, 2000.

**[0025]** ***Figure 5*** shows a comparison of the SCR domain structure of a number of complement control proteins and fragments thereof, the number of K+R residues, %K+R residues, pI, number of putative heparin binding sites, and ability to inhibit hemolysis and/or bind to heparin. Modified from Smith, SA, et al., *J. Virol.* 74(12), 5659-5666, 2000. The domains are SCR modules. Thus, for example, rVCP SCR (2, 3, 4), is a recombinantly produced polypeptide containing SCRs 2, 3, and 4 from VCP.

**[0026]** ***Figure 6*** shows the amino acid sequence of SPICE (SEQ ID NO: 44).

**[0027]** ***Figure 7*** shows the structure of compstatin and the structure of a compstatin analog showing increased complement inhibiting activity relative to compstatin. The figure also shows the IC50 of compstatin and the compstatin analog for inhibition of human complement. Amino acids 4 and 9 in the peptide chain depicted in the upper portion of the figure are as shown on the lower left for compstatin and as shown on the lower right for the compstatin analog. Thus the boxes labeled "X4" and "X9" in the peptide chain represent the side chains of the amino acids X4 and X9 shown in the lower portion of the figure for compstatin (left) and the compstatin analog (right) respectively.

**[0028]** ***Figure 8*** shows an exemplary compound for use in the invention.

**[0029]** ***Figure 9*** shows a needle/syringe assembly loaded with first and second therapeutic agents.

**Definitions**

**[0030]** "Activity period" refers to the time period over which a subject experiences an improvement in one or more symptoms and/or signs of a disorder following administration of a therapeutic agent, relative to a baseline condition or state existing prior to administration of the therapeutic agent. The activity period begins when the subject first experiences improvement and ends when the subject's condition or state returns to a baseline that existed prior to administration of the agent.

**[0031]** "Angiogenesis" or "angiogenic" refer to formation, growth, and/or development of new blood vessels.

**[0032]** The terms "angiogenesis inhibitor" and "antiangiogenic agent" are used interchangeably herein to refer to agents that are capable of inhibiting or reducing one or more processes associated with angiogenesis including, but not limited to, endothelial cell proliferation, endothelial cell survival, endothelial cell migration, differentiation of precursor cells into endothelial cells, and capillary tube formation.

**[0033]** "Antibody", as used herein, refers to an immunoglobulin or portion thereof that binds to an antigen. An antibody may be natural or wholly or partially synthetically produced. An antibody may be derived from natural sources, e.g., purified from an animal such as a rodent, rabbit, or chicken, that has been immunized with an antigen or a construct that encodes the antigen. An antibody may be a member of any immunoglobulin class, including any of the human classes: IgG, IgM, IgA, IgD, and IgE. An antibody of use in this invention may be an antibody fragment such as an Fab', $F(ab')_2$, scFv (single-chain variable) or other fragment that retains an antigen binding site, or a recombinantly produced scFv fragment, including recombinantly produced fragments that comprise an immunoglobulin antigen binding domain. See, e.g., Allen, T., *Nature Reviews Cancer*, Vol.2, 750-765, 2002, and references therein. Antibody fragments which contain the idiotype of the antibody molecule can be generated by known techniques. For example, $F(ab')_2$ fragments can be produced by pepsin digestion of the antibody molecule, Fab' fragments can be produced by reducing the disulfide bridges of the $F(ab')_2$ fragment, or by treating the antibody molecule with papain and a reducing agent. An antibody can be an antibody multimer or a multimer of antibody fragments. Antibodies, antibody fragments, and/or protein domains comprising an antigen binding site may be generated and/or selected *in vitro*, e.g., using techniques such as phage display (Winter, G. et al., *Annu. Rev. Immunol.* 12:433-455, 1994), ribosome display (Hanes, J., and Pluckthun, A. *Proc. Natl. Acad. Sci. USA.* 94:4937-4942, 1997), etc.

**[0034]** An antibody may be polyclonal (e.g., an affinity-purified polyclonal antibody) or monoclonal. A "monoclonal antibody" as used herein refers to a population of substantially homogeneous antibodies or a member of such a population, i.e., the individual antibodies comprising the population are identical except for possible naturally occurring mutations that can be present in minor amounts. In contrast to polyclonal antibody preparations that typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen and is therefore highly specific. The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, monoclonal antibodies to be used in accordance with the present invention can be made by the hybridoma method first described by Kohler & Milstein, *Nature* 256: 495, 1975, or alternatively can be made by recombinant DNA methods (see e.g., U.S. Pat. No. 4,816,567).

**[0035]** An antibody may be a "chimeric" antibody in which for example, a variable domain of rodent origin is fused to a constant domain of human origin, thus retaining the specificity of the rodent antibody. The domain of human origin need not originate directly from a human in the sense that it is first synthesized in a human being. Instead, "human" domains may be generated in rodents whose genome incorporates human immunoglobulin genes. Such an antibody is considered at least partially "humanized". The degree to which an antibody is "humanized" can vary. Thus part or most of the variable domain of a rodent antibody may be replaced by human sequences, e.g., by site-directed mutagenesis of a polynucleotide that encodes the antibody or a portion thereof. According to one approach rodent, e.g., murine, complementarity-determining regions (CDRs) are grafted onto the variable light (VL) and variable heavy (VH) frameworks of human immunoglobulin molecules, while retaining only those rodent framework residues deemed essential for the integrity of the antigen-binding site. See Gonzales NR, *Tumour Biol.* Jan-Feb;26(1):31-43, 2005 for a review of various methods of minimizing antigenicity of a monoclonal antibody. Such human or humanized chimeric antibodies are often preferred for use in therapy of human diseases or disorders, since the human or humanized antibodies are less likely than to induce an immune response.

**[0036]** A variety of methods are known for determining whether or not an antibody reacts with, or specifically binds to, an antigen such and for determining the affinity of such binding if desired. Examples include enzyme-linked immunosorbent assays (ELISA), radioimmunoassays (RIA), and the like. Binding of an antibody to a target molecule such as a protein may inhibit or interfere with the activity of the target molecule. For example, binding of an antibody to ligand

such as a growth factor may interfere with the binding of the ligand to its receptor(s); binding of an antibody to a receptor may interfere with the binding of the receptor to its ligand(s).

**[0037]** The terms "approximately" or "about" in reference to a number include numbers that fall within a range of 5% in either direction (greater than or less than) of the number unless otherwise stated or otherwise evident from the context (except where such number would exceed 100% of a possible value).

**[0038]** "Biocompatible" refers to a material that is substantially nontoxic to a recipient's cells in the quantities and at the location used, and does not elicit or cause a significant deleterious or untoward effect on the recipient's body at the location used, e.g., an unacceptable immunological or inflammatory reaction, unacceptable scar tissue formation, etc. A material that is biocompatible with the eye does not substantially interfere with the physiology or function of the eye.

**[0039]** "Biodegradable" means that a material is capable of being broken down physically and/or chemically within cells or within the body of a subject, e.g., by hydrolysis under physiological conditions and/or by natural biological processes such as the action of enzymes present within cells or within the body, and/or by processes such as dissolution, dispersion, etc., to form smaller chemical species which can typically be metabolized and, optionally, used by the body, and/or excreted or otherwise disposed of. Preferably a biodegradable compound is biocompatible. A polymer whose molecular weight decreases over time *in vivo* due to a reduction in the number of monomers is considered biodegradable.

**[0040]** A "biological macromolecule" is a large molecule composed of smaller subunits of a type that are found in biological systems. Examples include polypeptides, nucleic acids, and polysaccharides. Typically a biological macromolecule contains at least 3 subunits (e.g., amino acids, nucleosides, monosaccharides, etc.). The biological macromolecule may be a naturally occurring polypeptide, nucleic acid, or polysaccharide. The biological macromolecule may be modified, e.g., it may be conjugated to a nonbiological molecule such as synthetic polymer, etc.

**[0041]** The phrases "characterized by macular degeneration, choroidal neovascularization, retinal neovascularization, or any combination of the foregoing" and "characterized by macular degeneration, choroidal neovascularization, or retinal neovascularization" are intended to indicate that macular degeneration, CNV, and/or RNV, is a characteristic (i.e., typical) feature of the disorder. Macular degeneration, CNV, and/or RNV may be a defining and/or diagnostic feature of the disorder.

**[0042]** "Choroidal neovascularization" (CNV) refers to the abnormal development, proliferation, and/or growth of blood vessels arising from the choriocapillaris. The blood vessels typically extend through Bruch's membrane, RPE layer, and/or subretinal space.

**[0043]** A "complement component" or "complement protein" is a molecule that is involved in activation of the complement system or participates in one or more complement-mediated activities. Components of the classical complement pathway include, e.g., C1q, C1r, C1s, C2, C3, C4, C5, C6, C7, C8, C9, and the C5b-9 complex, also referred to as the membrane attack complex (MAC) and active fragments or enzymatic cleavage products of any of the foregoing (e.g., C3a, C3b, C4a, C4b, C5a, etc.). Components of the alternative pathway include, e.g., factors B, D, H, and I, and properdin.

**[0044]** The terms "deliver" or "delivery", in the context of a drug delivery device or sustained release formulation refers to release of a therapeutic agent into its surrounding environment in the body.

**[0045]** A "drug delivery device" refers to a device, structure, or element that contains and/or delivers a therapeutic agent to a subject. Release of the drug may, but need not, occur as a result of degradation of the drug delivery device within the body. The term "drug delivery device" is used herein to refer to devices that contain a therapeutic agent and to devices that have not yet been loaded with the therapeutic agent. An ocular implant is a drug delivery device that has appropriate dimensions and structure for placement within the eye. Preferably an ocular drug delivery device does not substantially interfere with the physiology and/or functioning of the eye, e.g., the device causes minimal or no disruption of vision.

**[0046]** An "effective amount" of an active agent refers to the amount of the active agent sufficient to elicit a desired biological response. As will be appreciated by those of ordinary skill in this art, the absolute amount of a particular agent that is effective may vary depending on such factors as the desired biological endpoint, the agent to be delivered, the target tissue, *etc.* Those of ordinary skill in the art will further understand that an "effective amount" may be administered in a single dose, or may be achieved by administration of multiple doses. For example, an effective amount of a therapeutic agent for the treatment of an eye disorder may be an amount sufficient to treat the disorder, e.g., an amount sufficient to achieve one or more of the following: (i) inhibit or prevent drusen formation; (ii) cause a reduction in drusen number and/or size (drusen regression); (iii) cause a reduction in or prevent lipofuscin deposits; (iv) inhibit or prevent visual loss or slow the rate of visual loss; (v) inhibit choroidal neovascularization or slow the rate of choroidal neovascularization; (vi) cause a reduction in size and/or number of lesions characterized by choroidal neovascularization; (vii) inhibit choroidal

neovascularization or slow the rate of retinal neovascularization; (viii) cause a reduction in size and/or number of lesions characterized by retinal neovascularization; (ix) improve visual acuity and/or contrast sensitivity; (x) reduce macular edema and/or reduce abnormal macular thickness; (xi) inhibit or prevent photoreceptor or RPE cell atrophy or apoptosis, or reduce the rate of photoreceptor or RPE cell atrophy or apoptosis; (xii) inhibit or prevent progression of non-exudative macular degeneration to exudative macular degeneration.

**[0047]** "Eye disorder", which is used interchangeably herein with "ocular disorder" refers to any disease, disorder, or condition that involves or affects the eye or one or more portions, structures, or parts of the eye. The eye includes the eyeball, the periocular muscles, and the portion of the optic nerve which is within or adjacent to the eyeball.

**[0048]** "Exudative" macular degeneration is used herein synonymously with "wet" type macular degeneration, as those terms are generally understood in the art, i.e., to refer to a macular degeneration related condition such as ARMD characterized by neovascularization and/or the presence of an exudate.

**[0049]** "Identity" refers to the extent to which the sequence of two or more nucleic acids or polypeptides is the same. The percent identity between a sequence of interest and a second sequence over a window of evaluation, e.g., over the length of the sequence of interest, may be computed by aligning the sequences, determining the number of residues (nucleotides or amino acids) within the window of evaluation that are opposite an identical residue allowing the introduction of gaps to maximize identity, dividing by the total number of residues of the sequence of interest or the second sequence (whichever is greater) that fall within the window, and multiplying by 100. By gap is meant a portion of a sequence that is not occupied by a residue. For example, the sequence A K L - - - S I G (SEQ ID NO: 43) contains a gap of three residues. When computing the number of identical residues needed to achieve a particular percent identity, fractions are to be rounded to the nearest whole number. Percent identity can be calculated with the use of a variety of computer programs known in the art. For example, computer programs such as BLAST2, BLASTN, BLASTP, Gapped BLAST, etc., generate alignments and provide percent identity between a sequence of interest and sequences in any of a variety of public databases. The algorithm of Karlin and Altschul (Karlin and Altschul, *Proc. Natl. Acad. Sci. USA* 87:22264-2268, 1990) modified as in Karlin and Altschul, *Proc. Natl. Acad. Sci. USA* 90:5873-5877, 1993 is incorporated into the NBLAST and XBLAST programs of Altschul et al. (Altschul, et al., *J. Mol. Biol.* 215:403-410, 1990). To obtain gapped alignments for comparison purposes, Gapped BLAST is utilized as described in Altschul et al. (Altschul, et al. *Nucleic Acids Res.* 25: 3389-3402, 1997). When utilizing BLAST and Gapped

BLAST programs, the default parameters of the respective programs are used. A PAM250 or BLOSUM62 matrix may be used. See the Web site having URL www.ncbi.nlm.nih.gov for these programs. In a specific embodiment, percent identity of a sequence of interest and a second sequence is calculated using BLAST2 with default parameters.

**[0050]** "Invasive therapy" as used herein, is therapy that involves insertion of an instrument or device into the eye or orbit, e.g, entrance into or penetration of the eyeball or entry into the orbit by an instrument such as a needle, trocar, catheter, or the like.

**[0051]** "Liposomes" are artificial microscopic spherical particles formed by a lipid bilayer (or multilayers) enclosing an aqueous compartment. Liposomes can be used for delivering certain of the compositions of the invention.

**[0052]** The term "long-acting therapeutic agent" refers to a therapeutic agent that has an activity period of at least 3 months when administered in medically acceptable quantities. A "medically acceptable quantity" refers to an amount that does not cause unacceptable toxicity or adverse effects under the conditions of administration.

**[0053]** "Macular degeneration related condition" refers to any of a number of disorders and conditions in which the macula degenerates or loses functional activity. The degeneration or loss of functional activity can arise as a result of, for example, cell death, decreased cell proliferation, and/or loss of normal biological function. Macular degeneration can lead to and/or manifest as alterations in the structural integrity of the cells and/or extracellular matrix of the macula, alteration in normal cellular and/or extracellular matrix architecture, and/or the loss of function of macular cells. The cells can be any cell type normally present in or near the macula including RPE cells, photoreceptors, and/or capillary endothelial cells. ARMD is the major macular degeneration related condition. Others include Best macular dystrophy, Sorsby fundus dystrophy, Mallatia Leventinese and Doyne honeycomb retinal dystrophy.

**[0054]** "Non-exudative" macular degeneration is used herein synonymously with "dry" type macular degeneration as those terms are generally used in the art, to refer to a macular degeneration related condition, e.g., ARMD, in which neovascularization and/or exudation that would be detectable using standard methods such as fluorescein angiography has not occurred.

**[0055]** "Ocular implant" refers to a device or structure that has appropriate dimensions, shape, and/or configuration and is made of appropriate materials so that it may be placed in the eye without causing unacceptable interference with the physiology or functioning of the eye. Preferably placement of an ocular implant does not significantly disrupt vision. An ocular implant is typically a solid or semi-solid article of manufacture and is typically macroscopic, i.e., visible with the naked eye.

**[0056]** "Plurality" means more than one.

**[0057]** "Polypeptide", as used herein, refers to a polymer of amino acids, optionally including one or more amino acid analogs. A protein is a molecule composed of one or more polypeptides. A peptide is a relatively short polypeptide, typically between about 2 and 60 amino acids in length. The terms "protein", "polypeptide", and "peptide" may be used interchangeably. Polypeptides used herein may contain amino acids such as those that are naturally found in proteins, amino acids that are not naturally found in proteins, and/or amino acid analogs that are not amino acids. A large number of art-recognized analogs of the 20 amino acids commonly found in proteins (the "standard" amino acids) are known. As used herein, an "analog" of an amino acid may be a different amino acid that structurally resembles the amino acid (a "non-standard" amino acid) or a compound other than an amino acid that structurally resembles the amino acid. One or more of the amino acids in a polypeptide may be modified, for example, by the addition of a chemical entity such as a carbohydrate group, a phosphate group, a farnesyl group, an isofarnesyl group, a fatty acid group, a linker for conjugation, functionalization, or other modification, etc. Certain non-limiting suitable analogs and modifications are described in WO2004026328. The polypeptide may be acetylated, e.g., at the N-terminus and/or amidated, e.g., at the C-terminus.

**[0058]** The natural or other chemical modifications such as those described above can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. A given polypeptide may contain many types of modifications. Polypeptides may be branched or they may be cyclic, with or without branching. Polypeptides may be conjugated with, encapsulated by, or embedded within a polymer or polymeric matrix, dendrimer, nanoparticle, microparticle, liposome, or the like. Polypeptides of use in this invention may, for example, be purified from natural sources, produced *in vitro* or *in vivo* in suitable expression systems using recombinant DNA technology (e.g., by recombinant host cells or in transgenic animals or plants), synthesized through chemical means such as conventional solid phase peptide synthesis and/or methods involving chemical ligation of synthesized peptides (see, e.g., Kent, S., *J Pept Sci.*, 9(9):574-93, 2003 and U.S. Pub. No. 20040115774), or any combination of these. The term "polypeptide sequence" or "amino acid sequence" as used herein can refer to the polypeptide material itself and is not restricted to the sequence information (i.e. the succession of letters or three letter codes chosen among the letters and codes used as abbreviations for amino acid names) that biochemically characterizes a polypeptide. A polypeptide sequence presented herein is presented in an N-terminal to C-terminal direction unless otherwise indicated.

**[0059]** "Poxvirus" refers to a family of complex, double-stranded DNA viruses constituting the family *Poxviridae*. The family includes the orthopoxviruses, a genus of the family *Poxviridae*, subfamily *Chordopoxvirinae*, comprising many species infecting mammals. Poxviruses are described in Fields, BN, et al., Fields Virology, 3rd ed., Lippincott Williams & Wilkins, 2001. Orthopoxviruses include vaccinia virus, variola virus major, variola virus minor, cowpox virus, monkeypox virus, camelpox virus, swinepox virus, and ectromelia virus.

**[0060]** "Poxvirus complement control protein" refers to members of a family of homologous proteins encoded by a number of different poxviruses that bind to one or more complement pathway proteins and inhibit the classical pathway of complement activation, the alternative pathway of complement activation, the lectin pathway, or any combination of these. Poxvirus complement control proteins are members of the complement control protein (CCP), also called regulators of complement activation (RCA) superfamily (Reid, KBM and Day, AJ, *Immunol Today*, 10:177-80, 1989).

**[0061]** "Posterior segment of the eye" refers to the portion of the eye behind the lens, including the vitreous, choroid, and retina (including the macula).

**[0062]** "Rapid improvement in the condition of a subject's eye" refers to a clinically significant improvement in one or more symptoms and/or signs of an ocular disorder that occurs within two weeks, or preferably within one week, following administration of a therapeutic agent. Rapid improvement in the condition of a subject's eye can include, without limitation, any one or more of the following: increased visual acuity (e.g., gaining two or more lines of vision on a visual acuity chart), decreased visual distortion, increased contrast sensitivity, decreased retinal vessel leakage, decreased macular thickness (e.g., a decrease in macular thickness of at least 50% from a baseline value). In general, "rapid" as used herein in reference to a therapeutic or other biological effect, means occurring within two weeks or less following a reference event (e.g., administration of a therapeutic agent). In some embodiments, "rapid" means occurring within one week or less following a reference event.

**[0063]** "Retinal neovascularization" refers to the abnormal development, proliferation, and/or growth of blood vessels on or in the retina, e.g., on the retinal surface (i.e., as will be evident to one of ordinary skill in the art, the abnormal proliferation, and/or growth originates from blood vessels already present on or in the surface). "Retinal" here refers to the source of the neovascularization.

**[0064]** "Single procedure" means a procedure, i.e., a process or series of steps or acts that involves a single entrance into or penetration of the eyeball or entry into the orbit by an instrument such as a needle, trocar, catheter, or the like. For example, an eye injection, e.g., an

intravitreal injection, is a single procedure provided that the tip of the needle, once having been inserted into the eyeball, is not reintroduced into the eyeball once having been withdrawn therefrom. A single procedure may or may not involve multiple penetrations of one or more structures of the eye, e.g., the vitreous, provided that only a single entrance into or penetration of the eyeball takes place.

**[0065]** "Small molecule" refers to organic compounds, whether naturally-occurring or artificially created (*e.g.*, via chemical synthesis) that have relatively low molecular weight and that are not proteins, polypeptides, or nucleic acids. Typically, small molecules have a molecular weight of less than about 1500 g/mol and multiple carbon-carbon bonds.

**[0066]** "Specific binding" generally refers to a physical association between a target polypeptide (or, more generally, a target molecule) and a binding molecule such as an antibody or ligand. The association is typically dependent upon the presence of a particular structural feature of the target such as an antigenic determinant or epitope recognized by the binding molecule. For example, if an antibody is specific for epitope A, the presence of a polypeptide containing epitope A or the presence of free unlabeled A in a reaction containing both free labeled A and the binding molecule that binds thereto, will reduce the amount of labeled A that binds to the binding molecule. It is to be understood that specificity need not be absolute but generally relates to the context in which the binding occurs. For example, it is well known in the art that numerous antibodies cross-react with other epitopes in addition to those present in the target molecule. Such cross-reactivity may be acceptable depending upon the application for which the antibody is to be used. One of ordinary skill in the art will be able to select antibodies or ligands having a sufficient degree of specificity to perform appropriately in any given application (e.g., for detection of a target molecule, for therapeutic purposes, etc). It is also to be understood that specificity may be evaluated in the context of additional factors such as the affinity of the binding molecule for the target versus the affinity of the binding molecule for other targets, e.g., competitors. If a binding molecule exhibits a high affinity for a target molecule that it is desired to detect and low affinity for nontarget molecules, the antibody will likely be an acceptable reagent. Once the specificity of a binding molecule is established in one or more contexts, it may be employed in other, preferably similar, contexts without necessarily re-evaluating its specificity. Binding of two or more molecules may be considered specific if the affinity (equilibrium dissociation constant, Kd) is $10^{-3}$ M or less, preferably $10^{-4}$ M or less, more preferably $10^{-5}$ M or less, e.g., $10^{-6}$ M or less, $10^{-7}$ M or less, $10^{-8}$ M or less, or $10^{-9}$ M or less under the conditions tested, e.g., under physiological conditions.

[0067] "Stabilize", as used herein in reference to a eye disorder, means to reduce the rate of progression of the disorder and/or to prevent or reduce the likelihood of a rapid and noticeable deterioration in the condition of an eye afflicted with the disorder.

[0068] "Subject", as used herein, refers to an individual to whom an agent is to be delivered, e.g., for experimental, diagnostic, and/or therapeutic purposes. Preferred subjects are mammals, e.g., , primates, or humans. A subject under the care of a physician or other health care provider may be referred to as a "patient".

[0069] "Substantial sequence homology" as applied to a sequence means that the sequence displays at least approximately 60% identity, desirably at least approximately 70% identity, more desirably at least approximately 80% identity, and most desirably at least approximately 90% identity relative to a reference sequence. When two or more sequences are compared, any of them may be considered the reference sequence. % identity can be calculated using a FASTA, BLASTN, or BLASTP algorithm. Default parameters may be used. A PAM250 or BLOSUM62 matrix may be used.

[0070] A "sustained release formulation" or "sustained delivery formulation" is a composition of matter that comprises a therapeutic agent as one of its components and further comprises or has one or more components, elements, or structures effective to provide sustained release of the therapeutic agent, optionally in part as a consequence of the physical structure of the formulation. In some embodiments the structure is provided at least in part by the therapeutic agent itself and, optionally, one or more substances present at the site of administration. Sustained release is release or delivery that occurs either continuously or intermittently over a period of time e.g., at least 1, 2, 4, or 6 weeks, at least 1, 2, 3, 4, 6, 8, 10, 12, 15, 18, or 24 months, or longer.

[0071] "Therapeutic agent" is used interchangeably herein with "drug", to refer to any pharmaceutically active agent useful for treating a disorder. The term includes any pharmaceutically acceptable salt, prodrug, salt of a prodrug, and such derivatives of an active agent as are known in the art or readily produced using standard methods known in the art. "Prodrug" refers to a precursor of a drug, wherein the prodrug is not itself pharmacologically active (or has a lesser or different activity than the desired activity of the drug) but is converted, following administration (e.g., by metabolism) into the pharmaceutically active drug. A therapeutic agent can be, without limitation, a small molecule or a biological macromolecule such as a protein (e.g., an antibody) or nucleic acid such as an aptamer, siRNA, etc.

[0072] "Treating", as used herein, refers to providing treatment, i.e, providing any type of medical or surgical management of a subject in order to reverse, alleviate, inhibit the progression

of, prevent or reduce the likelihood of a disease, disorder, or condition, or in order to reverse, alleviate, inhibit or prevent the progression of, prevent or reduce the likelihood of one or more symptoms or manifestations of a disease, disorder or condition. "Prevent" refers to causing a disease, disorder, condition, or symptom or manifestation of such not to occur. Treating can include administering an agent to the subject following the development of one or more symptoms or manifestations indicative of a condition such as macular degeneration or diabetic retinopathy, e.g., in order to reverse, alleviate, reduce the severity of, and/or inhibit or prevent the progression of the condition and/or to reverse, alleviate, reduce the severity of, and/or inhibit or one or more symptoms or manifestations of the condition. A composition of this invention can be administered to a subject who has developed an eye disorder such as exudative or non-exudative ARMD or diabetic retinopathy or is at increased risk of developing such a disorder relative to a member of the general population. A composition of this invention can be administered prophylactically, i.e., before development of any symptom or manifestation of the condition. Typically in this case the subject will be at risk of developing the condition.

**[0073]** "Unit dosage form" as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated (e.g., for a single eye); each unit containing a predetermined quantity of an active agent selected to produce the desired therapeutic effect, optionally together with a pharmaceutically acceptable carrier, which may be provided in a predetermined amount. The unit dosage form may be, for example, a volume of liquid (e.g,. a pharmaceutically acceptable carrier) containing a predetermined quantity of a therapeutic agent, a predetermined amount of a therapeutic agent in solid form, an ocular implant containing a predetermined amount of a therapeutic agent, a plurality of nanoparticles or microparticles that collectively contain a predetermined amount of a therapeutic agent, etc. It will be appreciated that a unit dosage form may contain a variety of components in addition to the therapeutic agent. For example, pharmaceutically acceptable carriers, diluents, stabilizers, buffers, preservatives, etc., may be included.

## Detailed Description of Certain Embodiments of the Invention

**[0074]** *I. Overview*

**[0075]** The present invention provides compositions, methods, articles of manufacture, and pharmaceutical packs or kits for the treatment of an eye disorder. In certain embodiments of the invention the eye disorder is characterized by macular degeneration, CNV, or RNV. Exemplary disorders that can be treated according to the invention include, but are not limited to, macular

degeneration related conditions, diabetic retinopathy, and retinopathy of prematurity. . While the concepts underlying the invention are described herein with particular reference totreatment of wet ARMD or other conditions characterized by CNV and/or RNV, they apply to a range of different ocular (and other) disorders.

**[0076]** The invention encompasses the recognition that eye care providers, e.g., ophthalmologists, are often relucant to administer a therapeutic agent, e.g., an angiogenesis inhibitor, using an invasive procedure such as intravitreal injection that is associated with the risk of a severe complication unless there is a significant likelihood that the therapy will cause rapid improvement in the condition of the patient's eye. There can be reluctance to use an invasive procedure to administer therapy that may possibly prevent or delay future deterioration or destabilization in an eye that is, at least from a symptomatic standpoint, relatively stable. Similarly, patients are often reluctant to undergo administration of a therapeutic agent using an invasive procedure associated with the risk of a severe complication unless they have recently experienced noticeable deterioration or destabilization in the condition of their eye(s) and there is a significant likelihood that administration of the therapeutic agent will result in rapid and/or noticeable improvement in the condition. Patients with an eye in a relatively stable condition are often reluctant to undergo an invasive procedure to administer a therapeutic agent that may halt or slow progress of the disorder if the procedure is associated with the risk of a severe complication.

**[0077]** As a consequence, when administration of a therapeutic agent involves an invasive procedure associated with a risk of a severe complication, patients may be treated on a symptom driven, case-by-case basis, rather than according to a predetermined, recommended dosing schedule that would at least in part involve administering the agent while the patient's condition is apparently stable, at least from a symptomatic standpoint. This appears to be the case even though following the predetermined, recommended dosing schedule may have the potential to delay or inhibit future destabilization or deterioration. It was observed that in one well known eye clinic, an angiogenesis inhibitor was administered to patients with exudative ARMD on a symptom driven basis, in response to a sudden deterioration or destabilization in the condition of a patient's eye or in response to the presence of exudation (e.g., hemorrhage), rather than according to a predetermined dosing schedule.

**[0078]** Clinical trials have demonstrated that certain angiogenesis inhibitors, e.g., Macugen and Lucentis, are of benefit in terms of important parameters such as visual acuity when administered as recommended, i.e., by repeated intravitreal administration of a solution containing the agent. For example, administration of certain angiogenesis inhibitors slows the

rate of visual loss and may lead to at least temporary improvement in visual acuity. Based on clinical trials, the recommended dosing interval for Lucentis is 4 weeks (see, e.g., Heier, J.S., et al., *Invest Opthalmol Vis Sci*, 44:e-abstract 972, 2003), while the recommended dosing interval for Macugen is 6 weeks (see, e.g., Gragoudas ES, N Engl J Med., 351(27):2805-16, 2004). Avastin, while currently not approved for treatment of eye disorders by the U.S. Food and Drug Administration has been approved for the treatment of certain cancers and is available for use in the eye. Since Lucentis and Avastin act in a similar manner by binding to VEGF isoforms, these agents may have similar therapeutic effects.

**[0079]** Repeated administration of angiogenesis inhibitors according to the dosing intervals described above could result in sustained improvement in the condition of the subject's eye by inhibiting further neovascularization and blood vessel leakage. However, given the risk associated with intravitreal injection, ophthalmologists appear reluctant to administer a therapy associated with significant risk while the patient's symptoms remain substantially stable. Similarly, patients appear reluctant to submit to a procedure with significant risk when their symptoms remain substantially stable.

**[0080]** Therefore, as a result of the desire to avoid intravitreal injections, angiogenesis inhibitors may not be administered according to the recommended or predetermined dosing intervals. Instead, in practice these agents may be administered on a symptomatic basis, e.g., after a subject has experienced a deterioration or destabilization in the condition of the eye such as an acute loss of visual acuity and/or presence of exudation relative to a baseline condition, e.g., relative to the improved condition that resulted following administration of the previous dose of the angiogenesis inhibitor. Such deterioration or destabilization can occur at a variable and unpredictable time following the initial improvement. Instead of retreating the patient with an angiogenesis inhibitor when the patient is symptomatically stable in an effort to prevent future deterioration or destabilization, at the possible risk of causing a severe complication, treatment may be postponed until the subject has actually experienced deterioration or destabilization such that treatment would be likely to result in a symptomatic improvement in addition to any possible preventive effect. Thus the desire to avoid intravitreal injection of an eye that is symptomatically stable has a significant and heretofore unappreciated effect on clinical practice. In essence, the risk/benefit ratio as perceived by opthalmologists and patients may dictate that intravitreal administration of angiogenesis inhibitors should be performed on an individualized basis, following deterioration or destabilization of a patient's eye, rather than according to a predetermined dosing interval of approximately 4 or 6 weeks. It is unclear whether treatment on a symptomatic basis will have a greater, lesser, or equivalent efficacy on a

long-term basis (e.g., over periods of a year or more) relative to treatment according to the recommended, predetermined dosing schedule. However, in view of the definite and known risk of complications associated with intravitreal injection, ophthalmologists and patients may be willing to forego the possible long-term increased benefit that could result from administering anti-angiogenic therapy at predetermined intervals of 4-6 weeks instead of on a symptomatic basis.

**[0081]** In summary, the inventors' observations suggest that ophthalmologists and patients are reluctant to accept the risks associated with intravitreal injection unless there is a significant likelihood that the therapy thus administered will result in a rapid improvement in the condition of the patient's eye. However, this mode of administration may not be optimal in terms of providing long term improvement in and/or stabilization of the condition of the subject's eye.

**[0082]** The present invention encompasses the recognition that symptom driven treatment may be less than optimal for preventing or delaying further deterioration in the patient's condition. Furthermore, a formulation of a therapeutic agent that is preferred or optimal for producing rapid improvement in the condition of a patient's eye may not be preferred or optimal for achieving long-term improvement and/or stabilization. For example, in the case of eye disorders, rapid improvement may best be achieved by locally administering a therapeutic agent in solution or in a form in which it is quickly released, so as to rapidly achieve a high concentration of the agent at the location where activity is desired. However, long-term benefit may best be achieved by locally administering a sustained release formulation of the therapeutic agent that provides a lower, yet still therapeutically effective concentration of the therapeutic agent. Alternately or additionaly, therapeutic agent(s) that are most appropriate for relieving particular symptoms may be less appropriate for providing long-term benefit.

**[0083]** "Administering" or "administration" generally refers to introducing a therapeutic agent, composition, formulation, etc., to a desired site or location on or within the body of a subject, e.g., a site or location within the eye. Adminstration may be performed, e.g., by a health care provider. For purposes of convenience, the present specification refers generally toophthalmologists. However, the methods described herein, including both the methods of the invention and other methods (e.g., methods for diagnosing and/or monitoring an eye disorder) may be practeiced by any qualified health care provider.

**[0084]** The present invention provides compositions, methods, and articles of manufacture that address the preferences of opthalmologists and patients for avoiding procedures associated with a risk of severe complications while the condition of the subject's eye is relatively stable and at the same time offer the potential benefits associated with therapeutic agents and/or

formulations that may be preferred for long term improvement, stabilization, and/or reduced progression of the condition. In one aspect the invention provides a method of treating an eye disorder characterized by macular degeneration, CNV, or RNVcomprising the step of administering first and second therapeutic agents to the subject's eye in a single procedure, wherein the first therapeutic agent provides rapid improvement in the condition of the subject's eye and the second therapeutic agent is a long-acting therapeutic agent or is administered as a component of a sustained release formulation. One of skill in the art will appreciate that not all patients will exhibit an improvement in the condition of the eye. It will also be appreciated that the time to response (where "response" refers to improvement in the condition of the eye) may be an average time to response among patients who exhibit a response. In some embodiments of the invention, at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% of patients exhibit a rapid improvement. In some embodiments the response rate falls between 10% and 100%, or any intervening range such as between 30% and 80%, etc., exhibit a rapid improvement.

**[0085]** According to certain embodiments of the invention a procedure is used to administer a first therapeutic agent that provides rapid improvement in the condition of the subject's eye. The agent may be administered, e.g., following a sudden deterioration in the condition of the subject's eye such as may be caused by retinal hemorrhage or vessel leakage. In the course of the same procedure, a second therapeutic agent (which may be the same as or different from the first therapeutic agent) is also administered at little or no additional risk to the patient. The second therapeutic agent is a long-acting agent or is a component of a sustained release formulation (or both). The second therapeutic agent may provide a long-term benefit to the patient, preferably prolonging the time interval before the patient experiences destabilization or perceives significant deterioration in the condition of the eye.

**[0086]** The first and second therapeutic agents may be administered sequentially or they may be administered substantially at the same time. If administered sequentially, they may be administered in either order. The order may be selected based on the identity and formulation of the agents. In certain embodiments of the invention the first and second therapeutic agents are administered no more than 5, 10, 15, 30, or 45 seconds apart, or no more than 1, 2, 3, 4, 5, 10, 15, or 30 minutes apart. In other words, the time interval between completing administration of the first agent and completing administration of the second agent is no more than 5, 10, 15, 30, or 45 seconds or no more than 1, 2, 3, 4, 5, 10, 15, or 30 minutes apart in various embodiments of the invention. In certain embodiments of the invention administration of the first and second therapeutic agents is completed within 5, 10, 15, 30, or 45 seconds or within 1, 2, 3, 4, 5, 10, 15, or 30 minutes from the time at which any amount of either the first or second therapeutic agent

leaves the confines of any medical or surgical instrument or device (e.g., needle, syringe, trocar, catheter, cannula or other device that may enclose or contain a solution or solid formulation such as an implant and may be used to introduce such solution or solid formulation into the eye) and comes into contact with tissues or fluids of the subject's eye. Administration is said to be "complete" when the entire dose of an agent to be administered has left the confines of any medical or surgical instrument or device that is used to introduce the therapeutic agent into the subject's eye, it being understood that such instrument or device may retain a residual amount of the agent. The time interval starting from the time at which any amount of either the first or second therapeutic agent leaves the confines of any medical or surgical instrument or device and comes into contact with tissues or fluids of the subject's eye and the time at which administration of both first and second therapeutic agents is complete is referred to herein as the "time window" of administration. If more than two therapeutic agents are administered, the time window of administration is the time interval starting from the time at which any amount of any therapeutic agent leaves the confines of any medical or surgical instrument or device and comes into contact with tissues or fluids of the subject's eye and the time at which administration of all therapeutic agents is complete. The short time window of administration of the first and second therapeutic agents is an additional feature of the invention. Thus in a second aspect, the invention provides a method of treating an eye disorder characterized by macular degeneration, CNV, or RNV comprising the step of administering first and second therapeutic agents to the subject's eye within a short time window, wherein the first therapeutic agent provides rapid improvement in the condition of the subject's eye and the second therapeutic agent is a long-acting therapeutic agent or is administered as a component of a sustained release formulation. In various embodiments of the invention the time window is no more than 5, 10, 15, 30, or 45 seconds or no more than 1, 2, 3, 4, 5, 10, 15, or 30 minutes.

**[0087]** In yet another aspect, the invention provides a method of treating an eye disorder characterized by macular degeneration, CNV, or RNV comprising the step of administering first and second therapeutic agents to the subject's eye, wherein the first therapeutic agent is an angiogenesis inhibitor and the second therapeutic agent is a long-acting therapeutic agent or is administered as a component of a sustained release formulation. The second therapeutic agent may, but need not be, a complement inhibitor. In certain embodiments the second agent is a compstatin analog. Optionally the first and second therapeutic agents are administered in a single procedure.

**[0088]** In yet another aspect, the invention provides a method of treating an eye disorder characterized by macular degeneration, CNV, or RNV comprising the step of administering first

and second therapeutic agents to the subject's eye, wherein the second therapeutic agent is a complement inhibitor that is either a long-acting complement inhibitor or is administered as a component of a sustained release formulation. The first therapeutic agent may, but need not be, an angiogenesis inhibitor. Optionally the first and second therapeutic agents are administered in a single procedure.

**[0089]** The therapeutic agent that provides rapid improvement in the condition of the subject's eye may be administered in a liquid medium. In some embodiments the agent is administered at least in part in a formulation that releases the agent over time in sufficient amounts and sufficiently quickly to provide a rapid improvement in the condition of the subject's eye. For example, particles that degrade or otherwise release an effective amount of the agent within the first 24, 48, 72, or 96 hours, within the first week, or within the first 2 weeks following administration, could be used. In some embodiments a first portion of the agent is provided in solution and a second portion is provided in a formulation that provides for release over time. Optionally the second portion is a component of the sustained release preparation of the second agent.

**[0090]** By administering the first and second therapeutic agents in a single procedure, certain embodiments of the present invention minimize the overall risk of complications and make administration of the second therapeutic agent, which may primarily delay progression, inhibit further deterioration or destabilization, and/or provide slow rather than rapid improvement in the condition of the subject's eye more acceptable to ophthalmologists and/or patients. The combination therapy approach of the present invention thus provides an unexpected and unappreciated improvement in the risk/benefit ratio associated with invasive therapy of eye disorders.

**[0091]** The invention further provides pharmaceutical packs or kits and other articles of manufacture that facilitate the convenient, effective, and safe administration of multiple therapeutic agents to the eye using a single procedure.

**[0092]** In a specific embodiment the invention provides a method of treating exudative macular degeneration with a combination of a fast-acting anti-angiogenic drug and a sustained release or long-acting complement inhibiting drug. The fast-acting anti-angiogenic drug reduces the leakage and/or promotes regression of newly-formed blood vessels in the weeks following treatment; the slow-release or long-acting complement inhibiting drug will prevent the formation of new blood vessels and promote disease regression for significant amounts of time (months or years depending on the device or formulation). Thus in certain embodiments the therapeutic methods of the invention (1) inhibit/stop blood vessel formation and/or leakage in patients with

exudative macular degeneration in an acute fashion, so that the retina comes closer in proximity to the choroid layer of the eye, and that thus ischemic damage to the retina is reduced, and (2) install a slow-release or long-acting complement inhibitor that will lower the inflammatory response in the retina/RPE/choroid layers of the eye and thus block a primary stimulus for blood vessel growth and, optionally, inhibit the formation of drusen deposits in addition.

**[0093]** In certain embodiments of any aspect of the invention, administration of the first therapeutic agent does not result in rapid improvement in the condition of the subject's eye. However, improvement takes place more gradually, e.g., within 15 days to 3 weeks, within 15 days to 4 weeks, within 15 days to 5 weeks, or within 15 days to 6 weeks.

**[0094]** ***II. Therapeutic Agents***

**[0095]** A variety of different therapeutic agents are of use in the present invention. The first and second therapeutic agents may be the same or different. Furthermore, the invention is not limited to the administration of two therapeutic agents. Instead, any number of therapeutic agents can be administered in a single procedure. For example, the invention may comprise administering a composition comprising one or more therapeutic agents in solution in a liquid medium, e.g., an aqueous medium, and also administering a composition comprising or consisting essentially of a sustained release formulation, e.g., an ocular implant, comprising one or more therapeutic agents, in the course of the same procedure. Thus certain embodiments of the invention involve administering at least two, three, or four therapeutic agents in a liquid composition and at least two, three, or four therapeutic agents in a sustained release preparation. Any of the therapeutic agents described herein may be included in either or both of the liquid composition and the sustained release formulation. The sustained release formulation may be a liquid composition as long as it possesses sustained release properties. In specific embodiments the liquid composition contains two angiogenesis inhibitors or an angiogenesis inhibitor and a complement inhibitor. In specific embodiments the sustained release formulation contains two angiogenesis inhibitors, an angiogenesis inhibitor and a complement inhibitor, or two complement inhibitors. Optionally one or more additional therapeutic agents are included. In certain embodiments of the invention the sustained release formulation comprises compstatin or an analog thereof and a C5a receptor antagonist. In certain embodiments of the invention the sustained release formulation comprises compstatin or an analog thereof and a C3a receptor antagonist. In certain embodiments of the invention a liquid composition comprises compstatin or an analog thereof and a C5a receptor antagonist. In certain embodiments of the invention a liquid composition comprises compstatin or an analog thereof and a C3a receptor antagonist.

[0096] A therapeutic agent may be a small molecule or a biological macromolecule such as a protein, peptide, nucleic acid, etc. Classes of therapeutic agents of use in various embodiments of the present invention include, but are not limited to, angiogenesis inhibitors, complement inhibitors, anti-inflammatory agents, anti-infective agents (e.g., antibiotics, antivirals, antifungals), immunomodulators (e.g., immunosuppressive agents), anti-histamines, anesthetics or other pain relieving agents, beta-blockers, etc., it being understood that certain agents may be members of more than one class. In certain embodiments of the invention the first therapeutic agent is one that rapidly reduces macular edema, exudation, and/or vascular permeability following its administration. In certain embodiments of the invention the second agent is one that reduces ocular inflammation, CNV, and/or RNV.

[0097] In certain embodiments the therapeutic agent has a targeting moiety either covalently or noncovalently attached thereto. The targeting moiety comprises a ligand that binds to a marker present on or at the surface of a target cell or other component such as a drusen constituent present at a site of desired activity. . The term "ligand" is used to refer to a moiety that specifically binds to a second moiety.

[0098] The total amount of each therapeutic agent used, and their concentrations, can vary. Exemplary, nonlimiting, doses are between .0001 mg/dose and 100 mg/dose for each eye to be treated, e.g., between .001 mg/dose and 100 mg/dose, between .01 mg/dose and 100 mg/dose, between .05 mg/dose and 50 mg/dose, between .1 mg/dose and 10 mg/dose, between 0.5 mg/dose and 5 mg/dose, between 1 mg/dose and 10 mg/dose, etc. (with all doses being approximate). Exemplary, nonlimiting concentrations of a therapeutic agent in a composition of the invention are between approximately .0001 mg and 100 mg of the therapeutic agent per milliliter of solution, e.g., the concentration may be between .001 and 100 mg/ml, between .01 and 50 mg/ml, between 0.01 and 50 mg/ml, between .1 and 10 mg/ml, etc., with all concentrations being approximate. In specific embodiments the dose of either or both the first or second therapeutic agents is, without limitation, exactly or approximately 0.1, 0.2, 0.25, 0.3, 0.4, 0.5, 0.6, 0.7, 0.75, 0.8, 0.9, 1.0, 2.0, 3.0, 4.0, or 5.0 mg or can fall within a range delimited by any two of the foregoing values. For example, in certain embodiments a sustained release formulation, e.g., an ocular implant, contains exactly or approximately 0.1, 0.2, 0.25, 0.3, 0.4, 0.5, 0.6, 0.7, 0.75, 0.8, 0.9, 1.0, 2.0, 3.0, 4.0, or 5.0 mg of a therapeutic agent or an amount that falls within a range delimited by any two of the foregoing values. If the therapeutic agent is one already approved or under study for use in the disorder, a conventional dose may be used, where "conventional" means a unit dose that has been previously shown to be effective and/or is accepted in the art when used as a single agent. For example, 0.5 mg of Lucentis or 0.3 mg of

Macugen may be administered. In other embodiments the dose is between 0.5 and 2 times a conventional dose.

**[0099]** The following sections describe a variety of therapeutic agents of use in the invention, but the invention is not limited to these agents or classes of agents or their mechanisms of action.

**[00100]** ***A. Angiogenesis Inhibitors***

**[00101]** In certain embodiments of the invention one or more of the therapeutic agents is an angiogenesis inhibitor. Some angiogenesis inhibitors are cytotoxic agents that damage or kill target cells (e.g., endothelial cells) or trigger an immune-mediated response that results in damage to or killing of target cells. A second group includes agents that do not substantially damage or kill endothelial cells but instead inhibit their proliferation, migration, capillary tube formation, differentiation of endothelial cells from precursors thereof, or other processes associated with angiogenesis. Angiogenesis inhibitors in either or both group can be used.

**[00102]** A variety of angiogenesis inhibitors have been developed. Vascular endothelial growth factor (VEGF) is one of the key regulators of angiogenesis. Other regulators include fibroblast growth factor 2, pigment epithelium derived growth factor (PEDF), angiopoietins, and extracellular growth factor molecules (see, e.g., Ng, E. and Adamis, A., *Can. J. Ophthalmol.*, 40:352-68, 2005 for discussion of angiogenesis inhibitors and molecules involved in angiogenesis). Any of these regulators and/or proteins with which they interact can be a target of an angiogenesis inhibitor. VEGF-A is an endothelial cell mitogen with the ability to stimulate angiogenesis *in vivo* (Leung DW, Cachianes G, Kuang W-J, Goeddel DV, Ferrara N, *Science*, 246:1306-1309, 1989). Other VEGF family members include VEGF-B, VEGF-C, and VEGF-D. VEGF-A promotes endothelial cell proliferation and survival as well as vascular permeability (Ng, *supra*, and references therein). VEGF-A exists in several different isoforms containing 121, 145, 165, 189, and 208 amino acids (in humans), of which $VEGF_{165}$ may be primarily responsible for pathological ocular neovascularization. A number of different receptors for VEGF exist, e.g., VEGFR-1, VEGFR-2, and VEGFR-3.

**[00103]** A variety of different agents that inhibit the activity and/or expression of VEGF, e.g., VEGF-A, or one or more VEGF receptors are of use in the present invention. Such agents are referred to herein as "anti-VEGF agents". Useful agents include antibodies, antibody fragments, and nucleic acids that bind to one or more VEGF isoforms or VEGF receptors. The binding may inhibit interaction of one or more VEGF isoforms with its receptor(s). Macugen (Pfizer, Eyetech) is a VEGF nucleic acid ligand (also referred to as an aptamer) that binds to and inhibits $VEGF_{165}$ (U.S. Pat. No. 6,051,698). Lucentis (Genentech) is a humanized antibody fragment

that binds and inhibits Vascular Endothelial Growth Factor A (VEGF-A) (Gaudreault, J., et al., *Invest Ophthalmol. Vis. Sci.* 46, 726-733 (2005) and references therein. Avastin (Genentech) is a full length humanized antibody that also binds to VEGF (reviewed in Ferrara, N. *Endocr Rev.*, 25(4):581-611, 2004).

**[00104]** Other angiogenesis inhibitors of use in the invention include combretastatin or a derivative or prodrug thereof such as Combretastatin A4 Prodrug (CA4P); VEGF-Trap (Regeneron Pharmaceuticals), a fusion protein containing extracellular domains of two VEGF receptors connnected to the Fc region of an antibody (U.S. Pat. No. 5,844,099); EVIZON™ (squalamine lactate); AG-013958 (Pfizer, Inc.); JSM6427 (Jerini AG), rapamycin (sirolimus) and analogs thereof, anecortave acetate and other anti-angiogenic steroids, etc.

**[00105]** In certain embodiments of the invention the angiogenesis inhibitor is an agent that inhibits expression of a one or more pro-angiogenic molecules through the cellular process referred to as RNA interference (RNAi), also referred to as "gene silencing" (Novina, C.D. and Sharp, P.A. (2004) "The RNAi revolution", *Nature*, 430, 161-164.). Such agents are referred to herein as RNAi agents and includesiRNA and shRNA. Typically, RNAi agents of use in the present invention are nucleic acids that include a double-stranded portion between about 17 and 29 nucleotides, e.g., 19-25, or 19 nucleotides, in length, one strand of which includes a portion (the "antisense" or "guide" strand) that is substantially or perfectly complementary (e.g., at least 70%, at least 80%, at least 90%, or 100% complementary) to a target gene over about 17-29 nucleotides, e.g., 19-25, or 19 nucleotides. Optionally the RNAi agent includes one or more single-stranded 3' overhangs. The presence of an RNAi agent in a cell typically results in sequence-specific degradation and/or translational repression of a target mRNA encoded by the target gene, thereby inhibiting its expression. RNAi agents and methods for their design and manufacture are well known in the art. See, e.g., Novina, *supra*, and references therein as well as U.S.S.N. 09/ 821,832 (U.S. Pub. No. 20020086356) and U.S.S.N. 10/832,248 (U.S. Pub. No. 20040229266). It will be appreciated that RNAi agents may consist entirely of nucleotides such as those found naturally in RNA and/or DNA or may comprise any of a wide variety of nucleotide analogs or may differ in other ways from the structure of naturally occurring RNA and DNA. See, e.g., U.S. Pub. Nos. 20030175950, 20040192626, 20040092470, 20050020525, 20050032733.

**[00106]** In certain embodiments of the invention the angiogenesis inhibitor is an RNAi agent, e.g., an siRNA, that inhibits expression of one or more VEGF isoforms (e.g., $VEGF_{165}$); or inhibits expression of a VEGF receptor (e.g., VEGFR1). One of ordinary skill in the art will be able to design appropriate RNAi agents based on the known sequences of these molecules (or

any other target pro-angiogenic molecule including, but not limited to, angiogenin, angiopoietin, fibroblast growth factors, PEDF, etc.), which are available in public databases, e.g., GenBank. In certain embodiments of the invention the RNAi agent, when administered to cells, e.g., endothelial cells, *in vitro* in an appropriate amount optionally together with uptake enhancing compounds such as lipids, inhibits expression of its target gene by at least 60%, at least 70%, at least 80%, at least 90%. In certain embodiments of the invention the RNAi agent, when administered to the eye in an appropriate amount, inhibits expression of its target gene by at least 60%, at least 70%, at least 80%, at least 90%, or more within at least one structure, tissue, or compartment of the eye, e.g., within the retina. Exemplary RNAi agents include, but are not limited to, the siRNA known as Cand5 (Acuity Pharmaceuticals), which inhibits expression of VEGF, Sirna-027 (Sirna Therapeutics), which inhibits expression of VEGFR-1, and siRNAs having a sequence that differs at 1, 2, or 3 positions from that of either Cand5 or Sirna-027. Additional sequences and structures of RNAi agents useful in the present invention are described in U.S.S.N. 10/294,228 (U.S. Pub. No. 20040018176), U.S.S.N. 10/764,957 (U.S. Pub. No. 20050054596). Additional nucleic acids that inhibit experssion of a target gene include antisense oligonucleotides and ribozymes (see, e.g., U.S. Pat. No. 6,818,447).

**[00107]** Other angiogenesis inhibitors include various endogenous or synthetic peptides such as angiostatin, arresten, canstatin, combstatin, endostatin, thrombospondin, and tumstatin. Other antiangiogenic molecules include thalidomide and its antiangiogenic derivatives such as iMiDs (Bamias A, Dimopoulos MA. Eur J Intern Med. 14(8):459-469, 2003; Bartlett JB, Dredge K, Dalgleish AG. *Nat Rev Cancer.* 4(4):314-22, 2004).

**[00108]** Administration of certain angiogenesis inhibitors, e.g., anti-VEGF agents such as Avastin or Lucentis by intravitreal injection results in a rapid improvement in the condition of a subject's eye. While not wishing to be bound by any theory, this rapid improvement may at least in part occur due to diminished vessel leakage and reduced macular edema. These effects may, at least in the short term (i.e., over the first 1-2 weeks following treatment), be at least as significant as any inhibition of blood vessel development or growth that occurs during this time period. Therapeutic agents that rapidly reduce macular edema may be of particular use to cause rapid improvement in the condition of a subject's eye. Since VEGF is an inducer of vascular permeability, anti-VEGF agents may be especially effective for these purposes. In a specific embodiment of the invention the first therapeutic agent is endostatin. Endostatin has the ability to reduce vascular permeability (see, e.g., Campochiaro, PA., *Expert Opin Biol Ther.*, 4(9):1395-402, 2004). In certain embodiments of the invention endostatin and an anti-VEGF agent, e.g., an antibody, antibody fragment, or aptamer that binds to VEGF or to a VEGF receptor are

administered. Either the first therapeutic agent, the second therapeutic agent, or both, may be selected from the group consisting of anti-VEGF agents and endostatin. Either or both agents may be contained in a liquid composition or a sustained release formulation.

**[00109]** ***B. Complement Pathways and Complement Inhibitors***

**[00110]** The complement system plays a crucial role in a number of physiological processes including the response to injury and defense against foreign entities such as infectious agents. The complement system is also known to play a role in a number of diseases (Makrides, SC, *Pharm Rev.*, 50(1): 59-87, 1998). The complement system comprises more than 30 serum and cellular proteins that are involved in two major pathways, known as the classical and alternative pathways (*Kuby Immunology*, 2000).

**[00111]** The classical pathway is usually triggered by binding of a complex of antigen and IgM or IgG antibody to C1 (though certain other activators can also initiate the pathway). Activated C1 cleaves C4 and C2 to produce C4a and C4b, in addition to C2a and C2b. C4b and C2a combine to form C3 convertase, which cleaves C3 to form C3a and C3b. Binding of C3b to C3 convertase produces C5 convertase, which cleaves C5 into C5a and C5b. C3a, C4a, and C5a are anaphylotoxins and mediate multiple reactions in the acute inflammatory response. C3a and C5a are also chemotactic factors that attract immune system cells such as neutrophils. C3 and C5 convertase activity is controlled by a number of endogenous members of the Regulators of Complement Activation (RCA) family, also called Complement Control Protein (CCP) family, which includes complement receptor type 1 (CR1; C3b:C4b receptor), complement receptor type 2 (CR2), membrane cofactor protein (MCP; CD46), decay-accelerating factor (DAF), factor H (fH), and C4b-binding protein (C4bp). RCA proteins are described in U.S. Pat. No. 6,897,290.

**[00112]** The alternative pathway is initiated by microbial surfaces and various complex polysaccharides. In this pathway, C3b, resulting from cleavage of C3, which occurs spontaneously at a low level, binds to targets on cell surfaces and forms a complex with factor B, which is later cleaved by factor D, resulting in a C3 convertase. Cleavage of C3 and binding of another molecule of C3b to the C3 convertase gives rise to a C5 convertase. C3 and C5 convertases of this pathway are regulated by CR1, DAF, MCP, and fH. The mode of action of these proteins involves either decay accelerating activity (i.e., ability to dissociate convertases), ability to serve as cofactors in the degradation of C3b or C4b by factor I, or both.

**[00113]** The C5 convertases produced in both pathways cleave C5 to produce C5a and C5b. C5b then binds to C6, C7, and C8 to form C5b-8, which catalyzes polymerization of C9 to form the C5b-9 membrane attack complex (MAC). The MAC inserts itself into target cell membranes

and causes cell lysis. Small amounts of MAC on the membrane of cells may have a variety of consequences other than cell death.

**[00114]** A third complement pathway, the lectin complement pathway is initiated by binding of mannose-binding lectin (MBL) and MBL-associated serine protease (MASP) to carbohydrates. In the human lectin pathway, MASP-1 and MASP-2 are involved in the proteolysis of C4, C2 and C3, leading to a C3 convertase described above.

**[00115]** Complement activity is regulated by various mammalian proteins referred to as complement control proteins (CCPs). These proteins differ with respect to ligand specificity and mechanism(s) of complement inhibition (Lisczewski, MK and Atkinson, JP, in *The Human Complement System in Health and Disease*, eds. Volanakis, JE and Frank, MM, Dekker, New York, pp. 149-66, 1998). They may accelerate the normal decay of convertases and/or function as cofactors for factor I, to enzymatically cleave C3b and/or C4b into smaller fragments. CCPs are characterized by the presence of multiple (typically 4-56) homologous motifs known as short consensus repeats (SCR), complement control protein (CCP) modules, or SUSHI domains (Reid, KBM and Day, AJ, *Immunol Today*, 10:177-80, 1989). These domains, consisting of approximately 50-70 amino acids, typically about 60 amino acids, are characterized by a conserved motif that includes four disulfide-bonded cysteines (two disulfide bonds), proline, tryptophan, and many hydrophobic residues. Figure 2 shows an SCR consensus sequence. Any particular SCR may differ from the consensus at one or more positions.

**[00116]** In certain embodiments of the present invention at least one of the therapeutic agents, e.g., the second therapeutic agent, is a complement inhibitor. In some embodiments of the invention the complement inhibitor inhibits complement activation, e.g., inhibits activation of one or more complement proteins. For example, it may inhibit cleavage of an inactive complement protein to its active form. Complement inhibitors of use in the invention include, but are not limited to, (i) viral or mammalian complement control or complement inhibiting proteins as well as fragments or variants thereof that retain the ability to inhibit complement; (ii) compstatin and derivatives thereof; (iii) complement receptor antagonists. The following sections describe complement inhibitors of use in various embodiments of the invention.

**[00117]** ***Compounds that Inhibit C3 Activation or Activity***

**[00118]** In certain embodiments of the invention the complement inhibitor inhibits activation of C3. Exemplary compounds include compounds that bind to C3 and inhibit its cleavage. In some embodiments the compound is a peptide. In some embodiments the peptide is cyclic. In some embodiments of particular interest the compound is a compstatin analog. Compstatin is a cyclic peptide identified using phage display that binds to complement component C3 and

inhibits complement activation. Compstatin inhibits cleavage of C3 to C3a and C3b by convertase. Since C3 is a central component of all three pathways of complement activation, compstatin and analogs thereof are able to inhibit activation of the converging protein of all three pathways. Without wishing to be bound by any theory, the ability of compstatin and analogs thereof to inhibit the alternative pathway of complement activation may contribute significantly to efficacy in certain of the disorders described herein.

**[00119]** The invention encompasses the recognition that compstatin and analogs thereof possess unique and unexpected advantages as compared with certain other complement inhibitors, particularly for sustained release, in a variety of eye disorders. The relatively low molecular weight (~1.6 kD) and various other properties of compstatin analogs facilitate their incorporation into sustained delivery formulations and devices suitable for providing therapeutic concentrations in the eye. In certain embodiments a compstatin analog is delivered in a sustained manner over a prolonged period of time such as 1-2 weeks, 2-4 weeks, 1-3 months, 3-6 months, 6-12 months, 1-2 years, 2-5 years, or 5-10 years.

**[00120]** Compstatin is described in U.S. Pat. No. 6,319,897. Compstatin has the sequence Ile- [Cys-Val-Val-Gln-Asp-Trp-Gly-His-His-Arg-Cys]-Thr (SEQ ID NO: 8), with the disulfide bond between the two cysteines denoted by brackets. It is an N-terminal cyclic region of a larger peptide (SEQ ID NO: 1 in U.S. Pat. No. 6,319,897) that also shows complement inhibiting activity. A number of fragments and variants of compstatin inhibit complement have been identified. See, e.g. SEQ ID NOs: 13, 15, 20, 21, and 22 in U.S. Pat. No. 6,319,897.

**[00121]** A variety of compstatin analogs that have higher complement inhibiting activity than compstatin have been synthesized. See WO2004/026328 (PCT/US2003/029653), Morikis, D., et al., *Biochem Soc Trans.* 32(Pt 1):28-32, 2004, Mallik, B., et al., *J. Med. Chem.*, 274-286, 2005, and/or in Katragadda, M., et al. *J. Med. Chem.*, 49: 4616-4622, 2006. Complement inhibiting peptides and peptidomimetics described therein can be used in the present invention.

**[00122]** As used herein, the term "compstatin analog" includes compstatin and any complement inhibiting analog thereof and is used interchangeably with "compstatin derivative". The term "compstatin analog" encompasses compstatin and other compounds designed or identified based on compstatin and whose complement inhibiting activity is at least 50% as great as that of compstatin as measured, e.g., using any complement activation assay accepted in the art or substantially similar or equivalent assays. Certain compstatin analogs and suitable assays are described in U.S. Pat. No. 6,319,897, WO2004/026328, Morikis, *supra*, Mallik, *supra*, and/or Katragadda 2006, *supra*. The assay may, for example, measure alternative pathway-mediated erythrocyte lysis or be an ELISA assay (see Examples 5 and 6 of copending

applications USSN 11/544,389 and PCT/US06/39397). The invention includes embodiments in which any one or more of the compstatin analogs or compositions described herein is used in any the methods of treatment described herein. In certain embodiments of the invention a peptide having higher complement inhibiting activity than compstatin, e.g., at least 5-fold higher activity, at least 10-fold higher activity, etc., is used.

**[00123]** Compstatin and any of its analogs may be acetylated or amidated, e.g., at the N-terminus and/or C-terminus. For example, compstatin and any of its analogs may be acetylated at the N-terminus and amidated at the C-terminus. Consistent with usage in the art, "compstatin" as used herein, and the activities of compstatin analogs described herein relative to that of compstatin, refer to compstatin amidated at the C-terminus (Mallik, 2005, *supra*).

**[00124]** Concatamers or multimers of a compstatin analog thereof are also of use in the present invention. A supramolecular complex comprising a compstatin analog is of use in the methods of the invention.

**[00125]** The activity of a compstatin analog may be expressed in terms of its $IC_{50}$ (the concentration of the compound that inhibits complement activation by 50%), e.g., at a particular plasma concentration, with a lower $IC_{50}$ indicating a higher activity as recognized in the art. The activity of a preferred compstatin analog for use in the present invention is at least as great as that of compstatin. Certain modifications are known to reduce or eliminate complement inhibiting activity and may be explicitly excluded from any embodiment of the invention. The $IC_{50}$ of compstatin has been reported as 12 μM using a complement activity assay comprising measuring alternative pathway-mediated erythrocyte lysis assay (WO2004/026328). In one embodiment, the $IC_{50}$ of the compstatin analog is no more than the $IC_{50}$ of compstatin. In certain embodiments of the invention the activity of the compstatin analog is between 2 and 99 times that of compstatin (i.e., the analog has an $IC_{50}$ that is less than the $IC_{50}$ of compstatin by a factor of between 2 and 99). For example, the activity may be between 10 and 50 times as great as that of compstatin, or between 50 and 99 times as great as that of compstatin. In certain embodiments of the invention the activity of the compstatin analog is between 99 and 264 times that of compstatin. For example, the activity may be 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, or 264 times as great as that of compstatin. In certain embodiments the activity is between 264 and 300, 300 and 350, 350 and 400, or 400 and 500 times as great as that of compstatin. The invention further contemplates compstatin analogs having activities between 500 and 1000 times that of compstatin.

**[00126]** The $K_d$ of compstatin binding to C3 has been reported as 1.3 μM using isothermal titration calorimetry (Katragadda, et al., *J. Biol. Chem.*, 279(53), 54987-54995, 2004). Binding affinity of a variety of compstatin analogs for C3 has been correlated with their activity, with a lower $K_d$ indicating a higher binding affinity, as recognized in the art. A linear correlation between binding affinity and activity was shown for certain analogs tested (Katragadda, 2004, *supra*; Katragadda 2006, *supra*). In certain embodiments of the invention the compstatin analog binds to C3 with a $K_d$ of between 0.1 μM and 1.0 μM, between 0.05 μmM and 0.1 μM, between 0.025 μM and 0.05 μM, between 0.015 μM and 0.025 μM, between 0.01 μM and 0.015 μM, or between 0.001 μM and 0.01μM. In certain embodiments the $IC_{50}$ of the compstatin analog is between about 0.2 μM and about 0.5 μM. In certain embodiments the $IC_{50}$ of the compstatin analog is between about 0.1 μM and about 0.2 μM. In certain embodiments the $IC_{50}$ of the compstatin analog is between about 0.05 μM and about 0.1 μM. In certain embodiments the $IC_{50}$ of the compstatin analog is between about 0.001 μM and about 0.05 μM.

**[00127]** Compounds "designed or identified based on compstatin" include, but are not limited to, compounds that comprise an amino acid chain whose sequence is obtained by (i) modifying the sequence of compstatin (e.g., replacing one or more amino acids of the sequence of compstatin with a different amino acid or amino acid analog, inserting one or more amino acids or amino acid analogs into the sequence of compstatin, or deleting one or more amino acids from the sequence of compstatin); (ii) selection from a phage display peptide library in which one or more amino acids of compstatin is randomized, and optionally further modified according to method (i); or (iii) identified by screening for compounds that compete with compstatin or any analog thereof obtained by methods (i) or (ii) for binding to C3 or a fragment thereof. Many useful compstatin analogs comprise a hydrophobic cluster, a β-turn, and a disulfide bridge.

**[00128]** In certain embodiments of the invention the sequence of the compstatin analog comprises or consists essentially of a sequence that is obtained by making 1, 2, 3, or 4 substitutions in the sequence of compstatin, i.e., 1, 2, 3, or 4 amino acids in the sequence of compstatin is replaced by a different standard amino acid or by a non-standard amino acid. In certain embodiments of the invention the amino acid at position 4 is altered. In certain embodiments of the invention the amino acid at position 9 is altered. In certain embodiments of the invention the amino acids at positions 4 and 9 are altered. In certain embodiments of the invention only the amino acids at positions 4 and 9 are altered. In certain embodiments of the invention the amino acid at position 4 or 9 is altered, or in certain embodiments both amino acids 4 and 9 are altered, and in addition up to 2 amino acids located at positions selected from

1, 7, 10, 11, and 13 are altered. In certain embodiments of the invention the amino acids at positions 4, 7, and 9 are altered. In certain embodiments of the invention amino acids at position 2, 12, or both are altered, provided that the alteration preserves the ability of the compound to be cyclized. Such alteration(s) at positions 2 and/or 12 may be in addition to the alteration(s) at position 1, 4, 7, 9, 10, 11, and/or 13. Optionally the sequence of any of the compstatin analogs whose sequence is obtained by replacing one or more amino acids of compstatin sequence further includes up to 1, 2, or 3 additional amino acids at the C-terminus. In one embodiment, the additional amino acid is Gly. Optionally the sequence of any of the compstatin analogs whose sequence is obtained by replacing one or more amino acids of compstatin sequence further includes up to 5, or up to 10 additional amino acids at the C-terminus. It should be understood that compstatin analogs may have any one or more of the characteristics or features of the various embodiments described herein, and characteristics or features of any embodiment may additionally characterize any other embodiment described herein, unless otherwise stated or evident from the context. In certain embodiments of the invention the sequence of the compstatin analog comprises or consists essentially of a sequence shown in the upper portion of Figure 7, in which X4 and X9 represent modifiable side chains.

**[00129]** Compstatin and certain compstatin analogs having somewhat greater activity than compstatin contain only standard amino acids ("standard amino acids" are glycine, leucine, isoleucine, valine, alanine, phenylalanine, tyrosine, tryptophan, aspartic acid, asparagine, glutamic acid, glutamine, cysteine, methionine, arginine, lysine, proline, serine, threonine and histidine). Certain compstatin analogs having improved activity incorporate one or more non-standard amino acids. Useful non-standard amino acids include singly and multiply halogenated (e.g., fluorinated) amino acids, D-amino acids, homo-amino acids, N-alkyl amino acids, dehydroamino acids, aromatic amino acids (other than phenylalanine, tyrosine and tryptophan), ortho-, meta- or para-aminobenzoic acid, phospho-amino acids, methoxylated amino acids, and α,α-disubstituted amino acids. In certain embodiments of the invention, a compstatin analog is designed by replacing one or more L-amino acids in a compstatin analog described elsewhere herein with the corresponding D-amino acid. Such compounds and methods of use thereof are an aspect of the invention. Exemplary non-standard amino acids of use include 2-naphthylalanine (2-Nal), 1-naphthylalanine (1-Nal), 2-indanylglycine carboxylic acid (2Ig1), dihydrotrpytophan (Dht), 4-benzoyl-L-phenylalanine (Bpa), 2-α-aminobutyric acid (2-Abu), 3-α-aminobutyric acid (3-Abu), 4-α-aminobutyric acid (4-Abu), cyclohexylalanine (Cha), homocyclohexylalanine (hCha), 4-fluoro-L- tryptophan (4fW), 5-fluoro-L-tryptophan (5fW), 6-

fluoro-L-tryptophan (6fW), 4-hydroxy-L-tryptophan (4OH-W), 5-hydroxy-L-tryptophan (5OH-W), 6-hydroxy-L-tryptophan (6OH-W), 1-methyl-L-tryptophan (1MeW), 4-methyl-L-tryptophan (4MeW), 5-methyl-L-tryptophan (5MeW), 7-aza-L-tryptophan (7aW), α-methyl-L-tryptophan (αMeW), β-methyl-L-tryptophan (βMeW), N-methyl-L-tryptophan (NMeW), ornithine (orn), citrulline, norleucine, γ-glutamic acid, etc.

**[00130]** In certain embodiments of the invention the compstatin analog comprises one or more Trp analogs (e.g., at position 4 and/or 7 relative to the sequence of compstatin). Exemplary Trp analogs are mentioned above. See also Beene, et. al. *Biochemistry* 41: 10262-10269, 2002 (describing, *inter alia*, singly- and multiply-halogenated Trp analogs); Babitzke & Yanofsky, *J. Biol. Chem.* 270: 12452-12456, 1995 (describing, *inter alia*, methylated and halogenated Trp and other Trp and indole analogs); and U.S. Patents 6,214,790, 6,169,057, 5,776,970, 4,870,097, 4,576,750 and 4,299,838. Other Trp analogs include variants substituted (e.g., by a methyl group) at the α or β carbon and, optionally, also at one or more positions of the indole ring. Amino acids comprising two or more aromatic rings, including substituted, unsubstituted, or alternatively substituted variants thereof, are of interest as Trp analogs.

**[00131]** In certain embodiments the Trp analog has increased hydrophobic character relative to Trp. For example, the indole ring may be substituted by one or more alkyl (e.g., methyl) groups. In certain embodiments the Trp analog participates in a hydrophobic interaction with C3. Such a Trp analog may be located, e.g., at position 4 relative to the sequence of compstatin. In certain embodiments the Trp analog comprises a substituted or unsubstituted bicyclic aromatic ring component or two or more substituted or unsubstituted monocyclic aromatic ring components.

**[00132]** In certain embodiments the Trp analog has increased propensity to form hydrogen bonds with C3 relative to Trp but does not have increased hydrophobic character relative to Trp. The Trp analog may have increased polarity relative to Trp and/or an increased ability to participate in an electrostatic interaction with a hydrogen bond donor on C3. Certain exemplary Trp analogs with an increased hydrogen bond forming character comprise an electronegative substituent on the indole ring. Such a Trp analog may be located, e.g., at position 7 relative to the sequence of compstatin.

**[00133]** In certain embodiments of the invention the compstatin analog comprises one or more Ala analogs (e.g., at position 9 relative to the sequence of compstatin), e.g., Ala analogs that are identical to Ala except that they include one or more $CH_2$ groups in the side chain. In certain embodiments the Ala analog is an unbranched single methyl amino acid such as 2-Abu.

In certain embodiments of the invention the compstatin analog comprises one or more Trp analogs (e.g., at position 4 and/or 7 relative to the sequence of compstatin) and an Ala analog (e.g., at position 9 relative to the sequence of compstatin).

**[00134]** In certain embodiments of the invention the compstatin analog is a compound that comprises a peptide that has a sequence of $(X'aa)_n$- Gln - Asp – Xaa – Gly-$(X"aa)_m$, (SEQ ID NO: 2) wherein each X'aa and each X"aa is an independently selected amino acid or amino acid analog, wherein Xaa is Trp or an analog of Trp, and wherein n>1 and m>1 and n+m is between 5 and 21. The peptide has a core sequence of Gln - Asp – Xaa – Gly, where Xaa is Trp or an analog of Trp, e.g., an analog of Trp having increased propensity to form hydrogen bonds with an H-bond donor relative to Trp but, in certain embodiments, not having increased hydrophobic character relative to Trp. For example, the analog may be one in which the indole ring of Trp is substituted with an electronegative moiety, e.g., a halogen such as fluorine. In one embodiment Xaa is 5-fluorotryptophan. Absent evidence to the contrary, one of skill in the art would recognize that any non-naturally occurring peptide whose sequence comprises this core sequence and that inhibits complement activation and/or binds to C3 will have been designed based on the sequence of compstatin. In an alternative embodiment Xaa is an amino acid or amino acid analog other than a Trp analog that allows the Gln - Asp – Xaa – Gly peptide to form a β-turn.

**[00135]** In certain embodiments of the invention the peptide has a core sequence of X'aa-Gln - Asp – Xaa – Gly (SEQ ID NO: 3), where X'aa and Xaa are selected from Trp and analogs of Trp. In certain embodiments of the invention the peptide has a core sequence of X'aa-Gln - Asp – Xaa – Gly (SEQ ID NO: 3), where X'aa and Xaa are selected from Trp, analogs of Trp, and other amino acids or amino acid analogs comprising at least one aromatic ring. In certain embodiments of the invention the core sequence forms a β-turn in the context of the peptide. The β–turn may be flexible, allowing the peptide to assume two or more conformations as assessed for example, using nuclear magnetic resonance (NMR). In certain embodiments X'aa is an analog of Trp that comprises a substituted or unsubstituted bicyclic aromatic ring component or two or more substituted or unsubstituted monocyclic aromatic ring components. In certain embodiments of the invention X'aa is selected from the group consisting of 2-napthylalanine, 1-napthylalanine, 2-indanylglycine carboxylic acid, dihydrotryptophan, and benzoylphenylalanine. In certain embodiments of the invention X'aa is an analog of Trp that has increased hydrophobic character relative to Trp. For example, X'aa may be 1-methyltryptophan. In certain embodiments of the invention Xaa is an analog of Trp that has increased propensity to

form hydrogen bonds relative to Trp but, in certain embodiments, not having increased hydrophobic character relative to Trp. In certain embodiments of the invention the analog of Trp that has increased propensity to form hydrogen bonds relative to Trp comprises a modification on the indole ring of Trp, e.g., at position 5, such as a substitution of a halogen atom for an H atom at position 5. For example, Xaa may be 5-fluorotryptophan.

**[00136]** In certain embodiments of the invention the peptide has a core sequence of X'aa-Gln - Asp – Xaa – Gly-X"aa (SEQ ID NO: 4), where X'aa and Xaa are each independently selected from Trp and analogs of Trp and X"aa is selected from His, Ala, analogs of Ala, Phe, and Trp. In certain embodiments of the invention X'aa is an analog of Trp that has increased hydrophobic character relative to Trp, such as 1-methyltryptophan or another Trp analog having an alkyl substituent on the indole ring (e.g., at position 1, 4, 5, or 6). In certain embodiments X'aa is an analog of Trp that comprises a substituted or unsubstituted bicyclic aromatic ring component or two or more substituted or unsubstituted monocyclic aromatic ring components. In certain embodiments of the invention X'aa is selected from the group consisting of 2-napthylalanine, 1-napthylalanine, 2-indanylglycine carboxylic acid, dihydrotryptophan, and benzoylphenylalanine. In certain embodiments of the invention Xaa is an analog of Trp that has increased propensity to form hydrogen bonds with C3 relative to Trp but, in certain embodiments, not having increased hydrophobic character relative to Trp. In certain embodiments of the invention the analog of Trp that has increased propensity to form hydrogen bonds relative to Trp comprises a modification on the indole ring of Trp, e.g., at position 5, such as a substitution of a halogen atom for an H atom at position 5. For example, Xaa may be 5-fluorotryptophan. In certain embodiments X"aa is Ala or an analog of Ala such as Abu or another unbranched single methyl amino acid. In certain embodiments of the invention the peptide has a core sequence of X'aa-Gln - Asp – Xaa – Gly-X"aa (SEQ ID NO: 4), where X'aa and Xaa are each independently selected from Trp, analogs of Trp, and amino acids or amino acid analogs comprising at least one aromatic side chain, and X"aa is selected from His, Ala, analogs of Ala, Phe, and Trp. In certain embodiments X"aa is selected from analogs of Trp, aromatic amino acids, and aromatic amino acid analogs.

**[00137]** In certain preferred embodiments of the invention the peptide is cyclic. The peptide may be cyclized via a bond between any two amino acids, one of which is $(X'aa)_n$ and the other of which is located within $(X"aa)_m$. In certain embodiments the cyclic portion of the peptide is between 9 and 15 amino acids in length, e.g., 10-12 amino acids in length. In certain embodiments the cyclic portion of the peptide is 11 amino acids in length, with a bond (e.g., a disulfide bond) between amino acids at positions 2 and 12. For example, the peptide may be 13

amino acids long, with a bond between amino acids at positions 2 and 12 resulting in a cyclic portion 11 amino acids in length.

**[00138]** In certain embodiments the peptide comprises or consists of the sequence X'aa1 - X'aa2 - X'aa3 - X'aa4 -Gln-Asp-Xaa-Gly- X"aa1- X"aa2- X"aa3- X"aa4- X"aa5 (SEQ ID NO: 5). In certain embodiments X'aa4 and Xaa are selected from Trp and analogs of Trp, and X'aa1, X'aa2, X'aa3, X"aa1, X"aa2, X"aa3, X"aa4, and X"aa5 are independently selected from among amino acids and amino acid analogs. In certain embodiments X'aa4 and Xaa are selected from aromatic amino acids and aromatic amino acid analogs. Any one or more of X'aa1, X'aa2, X'aa3, X"aa1, X"aa2, X"aa3, X"aa4, and X"aa5 may be identical to the amino acid at the corresponding position in compstatin. In one embodiment, X"aa1 is Ala or a single methyl unbranched amino acid. The peptide may be cyclized via a covalent bond between (i) X'aa1, X'aa2, or X'aa3; and (ii) X"aa2, X"aa3, X"aa4 or X"aa5. In one embodiment the peptide is cyclized via a covalent bond between X'aa2 and X"aa4. In one embodiment the covalently bound amino acid are each Cys and the covalent bond is a disulfide (S-S) bond. In other embodiments the covalent bond is a C-C, C-O, C-S, or C-N bond. In certain embodiments one of the covalently bound residues is an amino acid or amino acid analog having a side chain that comprises a primary or secondary amine, the other covalently bound residue is an amino acid or amino acid analog having a side chain that comprises a carboxylic acid group, and the covalent bond is an amide bond. Amino acids or amino acid analogs having a side chain that comprises a primary or secondary amine include lysine and diaminocarboxylic acids of general structure $NH_2(CH_2)_nCH(NH_2)COOH$ such as 2,3-diaminopropionic acid (dapa), 2,4-diaminobutyric acid (daba), and ornithine (orn), wherein n = 1 (dapa), 2 (daba), and 3 (orn), respectively. Examples of amino acids having a side chain that comprises a carboxylic acid group include dicarboxylic amino acids such as glutamic acid and aspartic acid. Analogs such as beta-hydroxy-L-glutamic acid may also be used.

**[00139]** In certain emboeiments, the compstatin analog is a compound that comprises a peptide having a sequence:

**[00140]** Xaa1 – Cys – Val – Xaa2 - Gln - Asp – Xaa2* - Gly – Xaa3 - His - Arg – Cys – Xaa4 (SEQ ID NO: 6); wherein:

Xaa1 is Ile, Val, Leu, $B^1$-Ile, $B^1$-Val, $B^1$-Leu or a dipeptide comprising Gly-Ile or $B^1$-Gly-Ile, and $B^1$ represents a first blocking moiety;

Xaa2 and Xaa2* are independently selected from Trp and analogs of Trp;

Xaa3 is His, Ala or an analog of Ala, Phe, Trp, or an analog of Trp;

Xaa4 is L-Thr, D-Thr, Ile, Val, Gly, a dipeptide selected from Thr-Ala and Thr-Asn, or a

tripeptide comprising Thr-Ala-Asn, wherein a carboxy terminal –OH of any of the L-Thr, D-Thr, Ile, Val, Gly, Ala, or Asn optionally is replaced by a second blocking moiety $B^2$; and the two Cys residues are joined by a disulfide bond.

**[00141]** In other embodiments Xaa1 is absent or is any amino acid or amino acid analog, and Xaa2, Xaa2*, Xaa3, and Xaa4 are as defined above. If Xaa1 is absent, the N-terminal Cys residue may have a blocking moiety $B^1$ attached thereto.

**[00142]** In another embodiment, Xaa4 is any amino acid or amino acid analog and Xaa1, Xaa2, Xaa2*, and Xaa3 are as defined above. In another embodiment Xaa4 is a dipeptide selected from the group consisting of: Thr-Ala and Thr-Asn, wherein the carboxy terminal –OH or the Ala or Asn is optionally replaced by a second blocking moiety $B^2$.

**[00143]** In any of the embodiments of the compstatin analog of SEQ ID NO: 6, Xaa2 may be Trp.

**[00144]** In any of the embodiments of the compstatin analog of SEQ ID NO: 6, Xaa2 may be an analog of Trp comprising a substituted or unsubstituted bicyclic aromatic ring component or two or more substituted or unsubstituted monocyclic aromatic ring components. For example, the analog of Trp may be selected from 2-naphthylalanine (2-Nal), 1-naphthylalanine (1-Nal), 2-indanylglycine carboxylic acid (Igl), dihydrotrpytophan (Dht), and 4-benzoyl-L-phenylalanine.

**[00145]** In any of the embodiments of the compstatin analog of SEQ ID NO: 6, Xaa2 may be an analog of Trp having increased hydrophobic character relative to Trp. For example, the analog of Trp may be selected from 1-methyltryptophan, 4-methyltryptophan, 5-methyltryptophan, and 6-methyltryptophan. In one embodiment, the analog of Trp is 1-methyltryptophan. In one embodiment, Xaa2 is 1-methyltryptophan, Xaa2* is Trp, Xaa3 is Ala, and the other amino acids are identical to those of compstatin.

**[00146]** In any of the embodiments of the compstatin analog of SEQ ID NO: 6, Xaa2* may be an analog of Trp such as an analog of Trp having increased hydrogen bond forming propensity with C3 relative to Trp, which, in certain embodiments, does not have increased hydrophobic character relative to Trp. In certain embodiments the analog of Trp comprises an electronegative substituent on the indole ring. For example, the analog of Trp may be selected from 5-fluorotryptophan and 6-fluorotryptophan.

**[00147]** In certain embodiments of the invention Xaa2 is Trp and Xaa2* is an analog of Trp having increased hydrogen bond forming propensity with C3 relative to Trp which, in certain embodiments, does not have increased hydrophobic character relative to Trp. In certain embodiments of the compstatin analog of SEQ ID NO: 6, Xaa2 is analog of Trp having

increased hydrophobic character relative to Trp such as an analog of Trp selected from 1-methyltryptophan, 4-methyltryptophan, 5-methyltryptophan, and 6-methyltryptophan, and and Xaa2* is an analog of Trp having increased hydrogen bond forming propensity with C3 relative to Trp which, in certain embodiments, does not have increased hydrophobic character relative to Trp. For example, in one embodiment Xaa2 is methyltryptophan and Xaa2* is 5-fluorotryptophan.

**[00148]** In certain of the afore-mentioned embodiments, Xaa3 is Ala. In certain of the afore-mentioned embodiments Xaa3 is a single methyl unbranched amino acid, e.g., Abu.

**[00149]** In certain embodiments the invention employs a compstatin analog of SEQ ID NO: 6, as described above, wherein Xaa2 and Xaa2* are independently selected from Trp, analogs of Trp, and other amino acids or amino acid analogs that comprise at least one aromatic ring, and Xaa3 is His, Ala or an analog of Ala, Phe, Trp, an analog of Trp, or another aromatic amino acid or aromatic amino acid analog.

**[00150]** In certain embodiments of the invention the blocking moiety present at the N- or C-terminus of any of the compstatin analogs described herein is any moiety that stabilizes a peptide against degradation that would otherwise occur in mammalian (e.g., human or non-human primate) blood or vitreous. For example, blocking moiety $B^1$ could be any moiety that alters the structure of the N-terminus of a peptide so as to inhibit cleavage of a peptide bond between the N-terminal amino acid of the peptide and the adjacent amino acid. Blocking moiety $B^2$ could be any moiety that alters the structure of the C-terminus of a peptide so as to inhibit cleavage of a peptide bond between the C-terminal amino acid of the peptide and the adjacent amino acid. Any suitable blocking moieties known in the art could be used. In certain embodiments of the invention blocking moiety $B^1$ comprises an acyl group (i.e., the portion of a carboxylic acid that remains following removal of the –OH group). The acyl group typically comprises between 1 and 12 carbons, e.g., between 1 and 6 carbons. For example, in certain embodiments of the invention blocking moiety $B^1$ is selected from the group consisting of: formyl, acetyl, proprionyl, butyryl, isobutyryl, valeryl, isovaleryl, etc. In one embodiment, the blocking moiety $B^1$ is an acetyl group, i.e., Xaa1 is Ac-Ile, Ac-Val, Ac-Leu, or Ac-Gly-Ile.

**[00151]** In certain embodiments of the invention blocking moiety $B^2$ is a primary or secondary amine ($-NH_2$ or $-NHR^1$, wherein R is an organic moiety such as an alkyl group).

**[00152]** In certain embodiments of the invention blocking moiety $B^1$ is any moiety that neutralizes or reduces the negative charge that may otherwise be present at the N-terminus at physiological pH. In certain embodiments of the invention blocking moiety $B^2$ is any moiety

that neutralizes or reduces the negative charge that may otherwise be present at the C-terminus at physiological pH.

**[00153]** In certain embodiments of the invention, the compstatin analog is acetylated or amidated at the N-terminus and/or C-terminus, respectively. A compstatin analog may be acetylated at the N-terminus, amidated at the C-terminus, and or both acetylated at the N-terminus and amidated at the C-terminus. In certain embodiments of the invention a compstatin analog comprises an alkyl or aryl group at the N-terminus rather than an acetyl group.

**[00154]** In certain embodiments, the compstatin analog is a compound that comprises a peptide having a sequence:

**[00155]** Xaa1 – Cys – Val – Xaa2 - Gln - Asp – Xaa2* - Gly – Xaa3 - His - Arg – Cys – Xaa4 (SEQ ID NO: 7); wherein:

Xaa1 is Ile, Val, Leu, Ac-Ile, Ac-Val, Ac-Leu or a dipeptide comprising Gly-Ile or Ac-Gly-Ile;

Xaa2 and Xaa2* are independently selected from Trp and analogs of Trp;

Xaa3 is His, Ala or an analog of Ala, Phe, Trp, or an analog of Trp;

Xaa4 is L-Thr, D-Thr, Ile, Val, Gly, a dipeptide selected from Thr-Ala and Thr-Asn, or a tripeptide comprising Thr-Ala-Asn, wherein a carboxy terminal –OH of any of L-Thr, D-Thr, Ile, Val, Gly, Ala, or Asn optionally is replaced by $-NH_2$; and

the two Cys residues are joined by a disulfide bond.

**[00156]** Xaa1, Xaa2, Xaa2*, Xaa3, and Xaa4 are as described above for the various embodiments of SEQ ID NO: 6. For example, in certain embodiments Xaa2* is Trp. In certain embodiments Xaa2 is an analog of Trp having increased hydrophobic character relative to Trp, e.g., 1-methyltryptophan. In certain embodiments Xaa3 is Ala. In certain embodiments Xaa3 is a single methyl unbranched amino acid.

**[00157]** In certain embodiments of the invention Xaa1 is Ile and Xaa4 is L-Thr.

**[00158]** In certain embodiments of the invention Xaa1 is Ile, Xaa2* is Trp, and Xaa4 is L-Thr.

**[00159]** In certain embodiments the invention utilizes a compstatin analog of SEQ ID NO: 7, as described above, wherein Xaa2 and Xaa2* are independently selected from Trp, analogs of Trp, other amino acids or aromatic amino acid analogs, and

Xaa3 is His, Ala or an analog of Ala, Phe, Trp, an analog of Trp, or another aromatic amino acid or aromatic amino acid analog.

**[00160]** In certain embodiments of any of the compstatin analogs described herein, Xaa3 is an analog of His.

**[00161]** Table 1 provides a non-limiting list of compstatin analogs useful in the present invention. The analogs are referred to in abbreviated form in the left column by indicating specific modifications at designated positions (1-13) as compared to the parent peptide, compstatin (amidated at the C-terminus). Unless otherwise indicated, peptides are amidated at the C-terminus. Bold text is used to indicate certain modifications. Activity relative to compstatin (in this case compstatin amidated at the C-terminus) is based on published data and assays described therein (WO2004/026326, Mallik, 2005; Katragadda, 2006). Where multiple publications reporting an activity were consulted, the more recently published value is used, and it will be recognized that values may be adjusted in the case of differences between assays. It will also be appreciated that the peptides listed in Table 1 are cyclized via a disulfide bond between the two Cys residues when used in the therapeutic compositions and methods of the invention.

[00162] Table 1

| Peptide | Sequence | SEQ ID NO: | Activity over compstatin |
|---|---|---|---|
| Compstatin | *H*-ICVVQDWGHHRCT-*CONH2* | 8 | * |
| Ac-compstatin | *Ac*-ICVVQDWGHHRCT-*CONH2* | 9 | 3xmore |
| Ac-V4Y/H9A | *Ac*-ICV**Y**QDWG**A**HRCT-*CONH2* | 10 | 14xmore |
| Ac-V4W/H9A –OH | *Ac*-ICV**W**QDWG**A**HRCT-*COOH* | 11 | 27xmore |
| Ac-V4W/H9A | *Ac*-ICV**W**QDWG**A**HRCT-*CONH2* | 12 | 45xmore |
| Ac-V4W/H9A/T13dT -OH | *Ac*-ICV**W**QDWG**A**HRC**dT**-*COOH* | 13 | 55xmore |
| Ac-V4(2-Nal)/H9A | *Ac*-ICV**(2-Nal)**QDWG**A**HRCT-*CONH2* | 14 | 99xmore |
| Ac V4(2-Nal)/H9A –OH | *Ac*-ICV**(2-Nal)**QDWG**A**HRCT-*COOH* | 15 | 38xmore |
| Ac V4(1-Nal)/H9A –OH | *Ac*-ICV**(1-Nal)**QDWG**A**HRCT-*COOH* | 16 | 30xmore |
| Ac-V42Igl/H9A | *Ac*-ICV**(2-Igl)**QDWG**A**HRCT-*CONH2* | 17 | 39xmore |
| Ac-V42Igl/H9A –OH | *Ac*-ICV**(2-Igl)**QDWG**A**HRCT-*COOH* | 18 | 37xmore |
| Ac-V4Dht/H9A –OH | *Ac*-ICV**Dht**QDWG**A**HRCT-*COOH* | 19 | 5xmore |
| Ac-V4(Bpa)/H9A –OH | *Ac*-ICV**(Bpa)**QDWG**A**HRCT-*COOH* | 20 | 49xmore |
| Ac-V4(Bpa)/H9A | *Ac*-ICV**(Bpa)**QDWG**A**HRCT-*CONH2* | 21 | 86xmore |
| Ac-V4(Bta)/H9A –OH | *Ac*-ICV**(Bta)**QDWG**A**HRCT-*COOH* | 22 | 65xmore |
| Ac-V4(Bta)/H9A | *Ac*-ICV**(Bta)**QDWG**A**HRCT-*CONH2* | 23 | 64xmore |
| Ac-V4W/H9(2-Abu) | *Ac*-ICV**W**QDWG(2-**Abu)**HRCT-*CONH2* | 24 | 64xmore |
| +G/V4W/H9A +AN –OH | *H*-**G**ICV**W**QDWG**A**HRCT**AN**-*COOH* | 25 | 38xmore |
| Ac-V4(5fW)/H9A | *Ac*-ICV**(5fW)**QDWG**A**HRCT- *CONH2* | 26 | 31xmore |
| Ac-V4(5-MeW)/H9A | *Ac*-ICV**(5-methyl-W)**QDWG**A**HRCT- *CONH2* | 27 | 67xmore |
| Ac-V4(1-MeW)/H9A | *Ac*-ICV**(1-methyl-W)**QDWG**A**HRCT- *CONH2* | 28 | 264xmore |
| Ac-V4W/W7(5fW)/H9A | *Ac*-ICV**W**QD**(5fW)**G**A**HRCT-*CONH2* | 29 | 121xmore |
| Ac-V4(5fW)/W7(5fW)/H9A | *Ac*-ICV**(5fW)**QD**(5fW)**G**A**HRCT- *CONH2* | 30 | NA |
| Ac-V4(5-MeW)/W7(5fW)H9A | *Ac*-ICV**(5-methyl-W)**QD**(5fW)**G**A**HRCT-*CONH2* | 31 | NA |
| Ac-V4(1MeW)/W7(5fW)/H9A | *Ac*-ICV**(1-methyl-W)**QD**(5fW)**G**A**HRCT-*CONH2* | 32 | 264xmore |

NA = not available

**[00163]** In certain embodiments of the compositions and methods of the invention the compstatin analog has a sequence selected from sequences 9-32. In certain embodiments of the compositions and methods of the invention the compstatin analog has a sequence selected from SEQ ID NOs: 14, 21, 28, 29, and 32. In certain embodiments of the compositions and methods of the invention the compstatin analog has a sequence selected from SEQ ID NOs: 30 and 31. In one embodiment of the compositions and methods of the invention the compstatin analog has a sequence of SEQ ID NO: 28. In one embodiment of the methods of the invention the compstatin analog has a sequence of SEQ ID NO: 32.

**[00164]** In other embodiments, compstatin analogs having sequences as set forth in Table 1, but where the Ac- group is replaced by an alternate blocking moiety $B^1$, as described above, are used. In other embodiments, compstatin analogs having sequences as set forth in Table 1, but

where the $-NH_2$ group is replaced by an alternate blocking moiety $B^2$, as described above, are used.

**[00165]** In one embodiment, the compstatin analog binds to substantially the same region of the β chain of human C3 as does compstatin. In one embodiment the compstatin analog is a compound that binds to a fragment of the C-terminal portion of the β chain of human C3 having a molecular weight of about 40 kDa to which compstatin binds (Soulika, A.M., et al., *Mol. Immunol.*, 35:160, 1998; Soulika, A.M., et al., *Mol. Immunol.* 43(12):2023-9, 2006). In certain embodiments the compstatin analog is a compound that binds to the binding site of compstatin as determined in a compstatin-C3 structure, e.g., a crystal structure or NMR-derived 3D structure. In certain embodiments the compstatin analog is a compound that could substitute for compstatin in a compstatin-C3 structure and would form substantially the same intermolecular contacts with C3 as compstatin. In certain embodiments the compstatin analog is a compound that binds to the binding site of a peptide having a sequence set forth in Table 1, e.g., SEQ ID NO: 14, 21, 28, 29, or 32 in a peptide-C3 structure, e.g., a crystal structure. In certain embodiments the compstatin analog is a compound that binds to the binding site of a peptide having SEQ ID NO: 30 or 31 in a peptide-C3 structure, e.g., a crystal structure. In certain embodiments the compstatin analog is a compound that could substitute for the peptide of SEQ ID NO: 9-32, e.g., SEQ ID NO: 14, 21, 28, or 32 in a peptide-C3 structure and would form substantially the same intermolecular contacts with C3 as the peptide. In certain embodiments the compstatin analog is a compound that could substitute for the peptide of SEQ ID NO: 30 or 31 in a peptide-C3 structure and would form substantially the same intermolecular contacts with C3 as the peptide.

**[00166]** One of ordinary skill in the art will readily be able to determine whether a compstatin analog binds to a fragment of the C-terminal portion of the β chain of C3 using routine experimental methods. For example, one of skill in the art could synthesize a photocrosslinkable version of the compstatin analog by including a photo-crosslinking amino acid such as *p*-benzoyl-L-phenylalanine (Bpa) in the compound, e.g., at the C-terminus of the sequence (Soulika, A.M., et al, *supra*). Optionally additional amino acids, e.g., an epitope tag such as a FLAG tag or an HA tag could be included to facilitate detection of the compound, e.g., by Western blotting. The compstatin analog is incubated with the fragment and crosslinking is initiated. Colocalization of the compstatin analog and the C3 fragment indicates binding. Surface plasmon resonance may also be used to determine whether a compstatin analog binds to the compstatin binding site on C3 or a fragment thereof. One of skill in the art would be able to

use molecular modeling software programs to predict whether a compound would form substantially the same intermolecular contacts with C3 as would compstatin or a peptide having the sequence of any of the peptides in Table 1, e.g., SEQ ID NO: 14, 21, 28, 29, or 32, or in other embodiments SEQ ID NO: 30 or 31.

**[00167]** Compstatin analogs may be prepared by various synthetic methods of peptide synthesis known in the art *via* condensation of amino acid residues, e.g., in accordance with conventional peptide synthesis methods, may be prepared by expression *in vitro* or in living cells from appropriate nucleic acid sequences encoding them using methods known in the art. For example, peptides may be synthesized using standard solid-phase methodologies as described in Malik, *supra*, Katragadda, *supra*, and/or WO2004026328. Potentially reactive moieties such as amino and carboxyl groups, reactive functional groups, etc., may be protected and subsequently deprotected using various protecting groups and methodologies known in the art. See, e.g., "Protective Groups in Organic Synthesis", 3rd ed. Greene, T. W. and Wuts, P. G., Eds., John Wiley & Sons, New York: 1999. Peptides may be purified using standard approaches such as reversed-phase HPLC. Separation of diasteriomeric peptides, if desired, may be performed using known methods such as reversed-phase HPLC. Preparations may be lyophilized, if desired, and subsequently dissolved in a suitable solvent, e.g., water. The pH of the resulting solution may be adjusted, e.g. to physiological pH, using a base such as NaOH. Peptide preparations may be characterized by mass spectrometry if desired, e.g., to confirm mass and/or disulfide bond formation. See, e.g., Mallik, 2005, and Katragadda, 2006.

**[00168]** The structure of compstatin is known in the art, and NMR structures for a number of compstatin analogs having higher activity than compstatin are also known (Malik, *supra*). Structural information may be used to design compstatin mimetics. In one embodiment, the compstatin mimetic is any compound that competes with compstatin or any compstatin analog (e.g., a compstatin analog whose sequence is set forth in Table 1) for binding to C3 or a fragment thereof (such as a 40 kD fragment of the β chain to which compstatin binds) and that has an activity equal to or greater than that of compstatin. The compstatin mimetic may be a peptide, nucleic acid, or small molecule. In certain embodiments the compstatin mimetic is a compound that binds to the binding site of compstatin as determined in a compstatin-C3 structure, e.g., a crystal structure or a 3-D structure derived from NMR experiments. In certain embodiments the compstatin mimetic is a compound that could substitute for compstatin in a compstatin-C3 structure and would form substantially the same intermolecular contacts with C3 as compstatin. In embodiments the compstatin mimetic is a compound that binds to the binding site of a peptide having a sequence set forth in Table 1, e.g., SEQ ID NO: 14, 21, 28, 29, or 32,

or in certain embodiments SEQ ID NO: 30 or 31, in a peptide-C3 structure. In certain embodiments the compstatin mimetic is a compound that could substitute for a peptide having a sequence set forth in Table 1, e.g., SEQ ID NO: 14, 21, 28, 29, or 32, or in certain embodiments SEQ ID NO: 30 or 31, in a peptide-C3 structure and would form substantially the same intermolecular contacts with C3 as the peptide. In certain embodiments the compstatin mimetic has a non-peptide backbone but has side chains arranged in a sequence designed based on the sequence of compstatin.

**[00169]** One of skill in the art will appreciate that once a particular desired conformation of a short peptide has been ascertained, methods for designing a peptide or peptidomimetic to fit that conformation are well known. See, *e.g.*, G.R. Marshall (1993), Tetrahedron, 49: 3547-3558; Hruby and Nikiforovich (1991), in Molecular Conformation and Biological Interactions, P. Balaram & S. Ramasehan, eds., Indian Acad. of Sci., Bangalore, PP. 429-455), Eguchi M, Kahn M., Mini Rev Med Chem., 2(5):447-62, 2002. Of particular relevance to the present invention, the design of peptide analogs may be further refined by considering the contribution of various side chains of amino acid residues, e.g., for the effect of functional groups or for steric considerations as described in the art for compstatin and analogs thereof, among others.

**[00170]** It will be appreciated by those of skill in the art that a peptide mimic may serve equally well as a peptide for the purpose of providing the specific backbone conformation and side chain functionalities required for binding to C3 and inhibiting complement activation. Accordingly, it is contemplated as being within the scope of the present invention to produce and utilize C3-binding, complement-inhibiting compounds through the use of either naturally-occurring amino acids, amino acid derivatives, analogs or non-amino acid molecules capable of being joined to form the appropriate backbone conformation. A non-peptide analog, or an analog comprising peptide and non-peptide components, is sometimes referred to herein as a "peptidomimetic" or "isosteric mimetic," to designate substitutions or derivations of a peptide that possesses much the same backbone conformational features and/or other functionalities, so as to be sufficiently similar to the exemplified peptides to inhibit complement activation. More generally, a compstatin mimetic is any compound that would position pharmacophores similarly to their positioning in compstatin, even if the backbone differs.

**[00171]** The use of peptidomimetics for the development of high-affinity peptide analogs is well known in the art. Assuming rotational constraints similar to those of amino acid residues within a peptide, analogs comprising non-amino acid moieties may be analyzed, and their conformational motifs verified, by means of the Ramachandran plot (Hruby & Nikiforovich 1991), among other known techniques. Virtual screening methods can be used to identify

compstatin mimetics that bind to C3. Such methods may comprise use of suitable algorithms to computationally dock, score, and optionally rank a plurality of candidate structures. Any of a wide variety of available software programs can be used to perform the virtual screening method. Exemplary programs useful for flexible molecular docking include DOCK 4.0, FlexX 1.8, AutoDock 3.0, GOLD 1.2, ICM 2.8, and more recent versions thereof.

**[00172]** One of skill in the art will readily be able to establish suitable screening assays to identify additional compstatin mimetics and to select those having desired inhibitory activities. For example, compstatin or an analog thereof could be labeled (e.g., with a radioactive or fluorescent label) and contacted with C3 in the presence of different concentrations of a test compound. The ability of the test compound to diminish binding of the compstatin analog to C3 is evaluated. A test compound that significantly diminishes binding of the compstatin analog to C3 is a candidate compstatin mimetic. For example, a test compound that diminishes steady-state concentration of a compstatin analog-C3 complex, or that diminishes the rate of formation of a compstatin analog-C3 complex by at least 25%, or by at least 50%, is a candidate compstatin mimetic. One of skill in the art will recognize that a number of variations of this screening assay may be employed. Compounds to be screened include natural products, libraries of aptamers, phage display libraries, compound libraries synthesized using combinatorial chemistry, etc. The invention encompasses synthesizing a combinatorial library of compounds based upon the core sequence described above and screening the library to identify compstatin mimetics. Any of these methods could also be used to identify new compstatin analogs having higher inhibitory activity than compstatin analogs tested thus far.

**[00173]** Other compounds, e.g., polypeptides, small molecules, monoclonal antibodies, aptamers, etc., that bind to C3 or C3a receptors (C3aR) are of use in certain embodiments of the invention. For example, U.S. Pat. No. 5,942,405 discloses C3aR antagonists. Aptamers that bind to and inhibit factor B may be identified using methods such as SELEX (discussed below). U.S. Pat. Pub. No. 20030191084 discloses aptamers that bind to C1q, C3 and C5. Also of use are RNAi agents that inhibit local expression of C3 or C3R.

**[00174]** ***Compounds that Inhibit Factor B Activation or Activity***

**[00175]** In certain embodiments the complement inhibitor inhibits activation of factor B. For example, the complement inhibitor may bind to factor B. Exemplary agents include antibodies, antibody fragments, peptides, small molecules, and aptamers. Exemplary antibodies that inhibit factor B are described in U.S. Pat. Pub. No. 20050260198. In certain embodiments the isolated antibody or antigen-binding fragment selectively binds to factor B within the third short consensus repeat (SCR) domain. In certain embodiments the antibody prevents formation of a

C3bBb complex. In certain embodiments the antibody or antigen-binding fragment prevents or inhibits cleavage of factor B by factor D. In certain embodiments the complement inhibitor is an antibody, small molecule, aptamer, or polypeptide that binds to substantially the same binding site on factor B as an antibody described in U.S. Pat. Pub. No. 20050260198. Use of peptides that bind to and inhibit factor B, which may be identified using methods such as phage display, is within the scope of the invention. Use of aptamers that bind to and inhibit factor B, which may be identified using methods such as SELEX, is within the scope of the invention. Also of use are RNAi agents that inhibit local expression of factor B.

**[00176]** ***Compounds that Inhibit Factor D Activity***

**[00177]** In certain embodiments the complement inhibitor inhibits factor D. For example, the complement inhibitor may bind to factor D. Exemplary agents include antibodies, antibody fragments, peptides, small molecules, and aptamers. Exemplary antibodies that inhibit factor D are described in U.S. Pat. No. 7,112,327. In certain embodiments the complement inhibitor is an antibody, small molecule, aptamer, or polypeptide that binds to substantially the same binding site on factor D as an antibody described in U.S. Pat. No. 7,112,327. Exemplary polypeptides that inhibit alternative pathway activation and are believed to inhibit factor D are disclosed in U.S. Pub. No. 20040038869. Use of peptides that bind to and inhibit factor D, which may be identified using methods such as phage display, is within the scope of the invention. Use of aptamers that bind to and inhibit factor D, which may be identified using methods such as SELEX, is within the scope of the invention. Also of use are RNAi agents that inhibit local expression of factor D.

**[00178]** ***Viral complement control proteins (VCCPs) and viral complement inhibiting proteins (VCIP)***

**[00179]** VCCPs and VCIPs encoded by members of the poxvirus or herpesvirus families are of use. The invention contemplates use of any of the agents described in U.S.S.N. 60/616,983, filed October 8, 2004, in U.S.S.N.11/247,886, filed Oct. 8, 2005, entitled VIRAL COMPLEMENT CONTROL PROTEINS FOR EYE DISORDERS, and/or in U.S.S.N. 60/751,771, and US 11/612,751, filed Dec. 19, 2005, and Dec. 19, 2006, respectively, entitled VIRAL COMPLEMENT CONTROL PROTEINS FOR EYE DISORDERS CHARACTERIZED BY INFLAMMATION. Poxviruses and herpesviruses are families of large, complex viruses with a linear double-stranded DNA genome, some of which infect animals and can cause a range of diseases, the most feared of which in humans is smallpox. Certain of these viruses encode a number of immunomodulatory proteins that are believed to play a role in pathogenesis by subverting one or more aspects of the normal immune response