

Injection Device

Field of the Invention

[001] The present invention relates to improvements in injection devices for delivering active agents to patients, particularly but not exclusively intravitreal injection devices.

Background to the Invention

[002] A great number of different injection devices exist and have been proposed over the decades. The most basic of such devices is the basic syringe with needle, barrel and plunger, with the needle being optionally covered with a cap, and the syringe potentially also being pre-filled. The needle could be an integral part of the syringe (i.e., being moulded with the barrel), or could be a separate part and be attached via a tight or nested fit, or via a snap or screw-type mechanism such as a Luer lock attachment.

[003] Such injection devices are potentially dangerous due to exposure of the patient and the injector to the needle during administration. Care is also needed to inject the correct dose of active agent to a patient and at the correct depth for efficacy and to avoid damage to other structures, such as in intravitreal injections.

[004] More recently devices with protective sheaths have been developed which keep the needle shielded at all times when not in use – the sheath is biased towards a shielding position and is pushed out of the way as the needle is pushed towards, and into the intended subject. Such sheaths, however, typically are not locked into place, so pushing of the used injection device against another surface may result in puncturing that surface, which may be a human surface, as well.

[005] Automatic injection devices have also been described which automatically dispense a predetermined amount of agent when pushed against a subject, and which may also have a biased sheath to ensure shielding of the needle when not injecting. Such injection devices are, however, generally designed to dispense one particular amount, regardless of the recipient's age, size, health or other physiological parameter (such as the Epi-pen®), and typically dispense the agent in an abrupt short burst, which may be undesirable in many circumstances, such as when, for example, injecting into the eye.

[006] Motorised injection devices have also been described which dispense desired amounts of agent, optionally as step-wise sequential injections. Such injection devices are, however, very complex and expensive, and are unsuitable for single use or disposable injection procedures.

[007] Exemplary injection devices for intraocular injection, including intravitreal injection are known. Intravitreal injection in particular can be complex, as the desired injection site is in the *pars plana*, about 3-4mm behind the sclerocorneal limbus. In addition, due to the sensitivity and delicacy of the injection area, fine modulation of the force needed to inject the medicine is necessary to reduce the risk for adverse effects. However, as many of the medicinal products typically utilized in ophthalmic procedures are biologic products, such products may be of a higher viscosity than other drug products typically used with exemplary autoinjector products, which further complicates dosing and delivery. As such, traditionally such injections have been performed by a physician using a standard syringe and a measuring device (placed on the eye, surrounding the cornea, and providing a spaced hole for placing the needle through).

[008] Exemplary, devices designed specifically for intravitreal injection typically utilize a spacing measuring device at the injection end of the device to correctly position the needle over the *pars plana*. However, such devices generally: do not sufficiently ensure the correct injection depth (which is important in intravitreal injection); do not lock a sheath over the needle once used or protect the needle fluid path and injection site from contamination; do not lend themselves to easily adjustable, accurate and automatic dosing; are complex, expensive and do not readily lend themselves to one-off or disposable injection procedures, or a combination of such disadvantages.

[009] It is an object of the present invention to provide an improved automatic injection device and system which addresses these challenges, including the provision of accurate, adjustable dosing and modulation of injection and delivery force to reduce risk to patients, improve clinical workflows, and improve procedure effectiveness.

Summary of the Invention

[010] According to a first embodiment of the present invention there is provided an injection device comprising an elongated housing having a proximal end and a distal end, the proximal end comprising an actuation mechanism, wherein: the elongated housing defines an inner lumen between the proximal and distal ends which is adapted to receive and hold a formulation chamber relative to the actuation mechanism, the formulation chamber also having corresponding proximal and distal ends, and having a stopper between its proximal and distal ends for retaining formulation in the formulation chamber; the actuation mechanism having corresponding proximal and distal ends, and comprises an actuation housing with a proximal end, and a distal end adapted for engaging the elongated housing, wherein the actuation mechanism includes a plunger, the distal end of the plunger engaging the stopper or being adapted to engage the stopper, the plunger being in communication with at least one driving spring which biases the plunger distally when the

actuation mechanism is primed for injection; wherein the plunger is held in position against the bias by at least one retention arm or toggle having at least one first surface adapted to engage an opposed complementary second surface to hold the plunger in a first unactuated position when the actuation mechanism is primed for injection, the first and second surfaces being held in an engaged position by a restrainer which translates from an unactuated position or configuration to an actuated position or configuration when triggered, thereby allowing uncoupling of the engagement between the first and second surfaces and release of the plunger to move distally.

[011] In certain embodiments the restrainer may translate from the unactuated position or configuration to the actuated position or configuration by a trigger mechanism activated when a needle connected to the injection device reaches a desired injection depth and may, for example, comprise a mechanism that moves the restrainer proximally or distally as the needle is inserted into a subject to release said retention arm or toggle as the needle reaches a desired depth of insertion. However, it is also contemplated that the restrainer may be translated from a retention arm or toggle-restraining position or configuration to a releasing position or configuration by a mechanism activated by a button which is pressed or slid when the needle is at the desired injection depth. Alternatively, once the restrainer is translated from a retention arm or toggle-restraining position or configuration to a releasing position or configuration, the retention arm or toggle may still remain in its unactuated position until a mechanism is activated by a button which is pressed or slid by an operator.

[012] In a particular embodiment, the elongated housing also comprises a sleeve which is at least proximally slidable between the elongated housing and the formulation chamber, and which slides proximally as a needle connected to the injection device is inserted into a subject. In particular aspects the sleeve is adapted to engage the restrainer such that proximal movement of the sleeve causes proximal movement of the restrainer, and wherein operatively, insertion of a needle connected to the injection device into a surface results in the sleeve sliding proximally and, as a result, the restrainer moves proximally to the actuated position or configuration, although it is also envisaged that proximal movement of the sleeve may move the restrainer distally (for example, by leveraging or other opposing/complementary mechanisms). In certain aspects, movement of the restrainer to a retention arm or toggle-releasing position results in release of the retention arm or toggle, distal movement of the plunger and delivery of formulation to a subject. However, it is also contemplated that the plunger may still be restrained from distal movement despite the restrainer being in a releasing position/configuration until another mechanism is triggered to a release mode by, for example, a manually activated button. The sleeve may be between the elongated housing

and a formulation chamber when received therein or be external to the elongated housing, or a combination thereof.

[013] In a particular aspect, the restrainer is in the unactuated position when distal and in the actuated position when proximal, so that operatively, the restrainer moves proximally as the sleeve is slid proximally relative to the elongated housing, thereby releasing the retention arm or toggle to uncouple the first and second surfaces allowing said driving spring to drive the plunger and the stopper distally.

[014] In certain aspects the retention arm or toggle is a retention toggle which has distal and proximal ends, and is connected to the plunger by a pivot point located between said distal and proximal ends. In certain aspects the first surface of the toggle may be in the form of an outwardly directed ledge adapted to engage an opposed complementary second surface in the form of an inwardly directed ledge on or connected to the actuation housing, the proximal end of the toggle including a surface adapted to engage a complementary surface of the restrainer. In certain aspects the outwardly directed ledge may be positioned between the pivot point and the proximal end of the toggle.

[015] In certain aspects the restrainer may be connected to, or form part of the proximal end of the sleeve. In other aspects the restrainer may be separate to the sleeve.

[016] In certain aspects, at least when in use, the distal end of the injection device may comprise a sheath enshrouding at least a distal portion of a needle assembly in fluid communication with the formulation chamber, the sheath being either an integral part of the sleeve or being adapted to engage the distal end of the sleeve, and being adapted to slide between the elongated housing and the formulation chamber. The sheath may be at least proximally slidable with respect to the needle so as to unsheath the needle during insertion of said needle into a subject during injection and, in the process, moves the sleeve proximally, resulting in proximal movement of the restrainer to a retention arm or toggle-releasing position, allowing release of the plunger.

[017] In certain aspects the sleeve and sheath are held in a needle enshrouding position by a second spring stressed between the actuation housing or the plunger and the sleeve, which is adapted to engage the second spring.

[018] In other aspects the sheath comprises a spring or other suitable biasing means of its own stressed between a distal portion of the sheath and the needle assembly to ensure the sheath covers the needle tip.

[019] In certain aspects the retention arm or toggle, once released, is adapted to stop the sleeve and sheath from proximal movement once the sleeve and sheath have returned to a needle-enshrouding position.

[020] The at least one retention arm or toggle may, in certain aspects, comprise at least one biased arm, said at least one biased arm being connected at one end to at least one of the proximal end of the actuation mechanism housing or, in a preferred embodiment, the proximal end of the plunger, the other end of said at least one biased arm comprising an inwardly directed ledge adapted to engage a complementary outwardly directed ledge on at least one of the plunger or, in a preferred embodiment, the actuation mechanism housing, said outwardly directed ledge being optionally formed as a groove in or a ridge on said plunger.

[021] This configuration of the injection device actuation mechanism is such that the force to move the restrainer proximally to release the retention arm or toggle can be lowered significantly compared to mechanisms where the retention arm or toggle are biased inwardly against the plunger. According to certain aspects of the present invention, the triggering force required to allow uncoupling of the engagement between the first and second surfaces and release of the plunger to move distally is inversely proportional to a value a/b , wherein a is the distance between the proximal end of the toggle and the pivot point and b is the adaxial extension distance between the edge of the first surface and the pivot point, allowing regulation of the triggering force by regulation of the value a/b .

[022] The retention arm or toggle may comprise biasing means as an integral component, or may be biased by biasing means attached to a separate component of the actuation mechanism. In certain aspects the at least one retention arm or toggle is biased by integral biasing means which, when the device is primed for injection, apply force against and away from the plunger. In other aspects the at least one retention arm or toggle is biased by biasing means connected to the plunger and which, when the device is primed for injection, apply force against the retention arm or toggle, away from the plunger.

[023] In certain aspects the actuation mechanism housing and the elongated housing may be detachable from one another to allow placement, removal or replacement of formulation chamber(s) into or from said elongated housing.

[024] In certain aspects the formulation chamber is pre-filled.

[025] In other aspects the formulation chamber is vacuum or voidless filled, in which case engagement of the plunger with the stopper and placement of the formulation chamber in the elongated housing and connection of the actuation housing to the elongated housing results in positive pressure within the formulation chamber. This configuration provides the advantage that when a needle is placed in fluid communication with the distal end of the formulation chamber, the positive pressure within the formulation chamber results in a small amount of fluid being expelled from the formulation chamber through the needle, the needle being thereby filled. This automatically primes the device with formulation and further prevents air or other fluid or contaminants from entering the formulation chamber.

[026] In certain aspects a needle assembly is attached to the formulation chamber and the distal end of the formulation chamber is adapted to have the needle assembly attached thereto.

[027] In other aspects a needle assembly is attached to the elongated housing and the distal end of the elongated housing is adapted to have a needle assembly attached thereto and allow fluid communication between the formulation chamber and the needle. This requires bridging of the elongated housing between sleeve leaves, such that the sleeve is slidable between the outer portion of the elongated housing and the inner needle assembly-engaging portion of the elongated housing. In particular aspects, the elongated housing comprises a sleeve which is at least proximally slidable between the elongated housing and the formulation chamber and is adapted to engage the restrainer such that proximal movement of the sleeve causes proximal movement of the restrainer and wherein, operatively, the distal end of the elongated housing comprises a needle assembly having a sheath enshrouding at least a distal portion of a needle in fluid communication with said formulation chamber, wherein the sheath is at least proximally slidable with respect to the needle so as to unsheath the needle during insertion of the needle into a subject, resulting in proximal sliding of the sleeve and proximal movement of the restrainer to the actuated position.

[028] In certain aspects the needle assembly is attached to the distal end of said formulation chamber or said elongated housing by means of a tight fit, snap, screw or a Luer lock mechanism.

[029] In alternative aspects the needle may form an integral part of at least the formulation chamber or be an integral part of the elongated housing.

[030] In a specific embodiment, in an injection device according to the invention, the elongated housing comprises a sleeve which is at least adapted to slide proximally between the elongated housing and the formulation chamber and is adapted to engage the restrainer such that proximal

movement of the sleeve causes proximal movement of the restrainer; the distal end of said elongated housing is connected to or is adapted to be connected to a needle assembly comprising a sheath, wherein said sheath is at least proximally slidable with respect to the needle so as to unsheath the needle during insertion of said needle into a subject and so as to slide said sleeve proximally, which results in proximal movement of said restrainer from the first unactuated position to the second actuated position; the plunger is held in position against said stress by a toggle with distal and proximal ends and connected to the plunger by a pivot point located between said distal and proximal ends and wherein said first surface is in the form of an outwardly directed ledge positioned between the pivot point and the proximal end and adapted to engage said opposed complementary second surface provided in the form of a complementary inwardly directed ledge on or connected to the actuation housing, the proximal end of the toggle comprising a surface adapted to engage a complementary surface of the restrainer when in the unactuated position.

[031] According to another embodiment of the present invention, there is provided an injection device comprising an elongated housing having a proximal end and a distal end, the proximal end comprising an actuation mechanism, wherein: the elongated housing defines an inner lumen between the proximal and distal ends which includes or is adapted to receive and hold a formulation chamber relative to said actuation mechanism, the formulation chamber also having corresponding proximal and distal ends, and having a stopper between its proximal and distal ends for retaining formulation in said formulation chamber; the actuation mechanism has corresponding proximal and distal ends, and comprises an actuation housing with a proximal end, and a distal end adapted for engaging said elongated housing, wherein the actuation mechanism includes a plunger, the distal end of the plunger engaging the stopper or being adapted to engage said stopper, and the plunger being in communication with at least one driving spring which biases the plunger distally when the actuation mechanism is primed for injection, wherein the plunger is held in position against the bias by a toggle which has distal and proximal ends, and is connected to the plunger by a pivot point located between the distal and proximal ends, the toggle having an outwardly directed ledge positioned between the pivot point and the proximal end and adapted to engage an opposed inwardly directed ledge on or connected to the actuation housing to hold the plunger in a first unactuated position when the actuation mechanism is primed for injection, the proximal end of the toggle including a surface adapted to engage a complementary surface of a restrainer to hold the toggle in an unactuated position and thereby keep the outwardly directed ledge and opposed inwardly directed ledge in an engaged position, wherein the restrainer translates from an unactuated position or configuration to an actuated position or configuration when triggered, thereby allowing the toggle to deflect to an actuated position thereby uncoupling of the

engagement between the outwardly directed ledge and opposed inwardly directed ledge and release of the plunger to move distally; the elongated housing comprises a sleeve which is at least adapted to slide proximally between the elongated housing and the formulation chamber and is adapted to engage the restrainer such that proximal movement of the sleeve causes proximal movement of the restrainer; and the distal end of the elongated housing is connected to or is adapted to be connected to a needle assembly comprising a sheath, the sheath being either an integral part of said sleeve or being adapted to engage the distal end of the sleeve, wherein the sheath is at least proximally slidable with respect to the needle so as to unsheath the needle during insertion of the needle into a subject and so as to slide the sleeve proximally, which results in proximal movement of the restrainer from the unactuated position to the actuated position, uncoupling of the engagement between the outwardly directed ledge and opposed inwardly directed ledge, and release of the plunger to move distally.

[032] In certain aspects the actuation housing comprises a dosing mechanism which is adjustably coupled to the plunger at the proximal end of the actuation housing, such that a distance between the dosing mechanism and the actuation housing, and therefore an allowable travel distance of the plunger, can be set to a specified value, so that a selected volume of formulation may be operatively dispensed.

[033] In alternative aspects the plunger has a proximal end that extends proximally beyond the actuation housing and engages with a cap or knob via adjustable means, such that a distance between the cap or knob and the actuation housing, and therefore the allowable travel distance of the plunger is controlled, so that operatively adjustment of the cap allows delivery of a selected volume of formulation. In one specific aspect the dosing mechanism comprises a first internal knob, a second, external dose setting knob, and a dose delivery housing adapted to sit on the proximal end of the actuation housing, wherein the proximal end of the plunger engages with the first knob via a thread with axial:longitudinal pitch X, the first knob engages with the second knob axially, but not longitudinally, and the second external dose setting knob engages with the dose delivery housing via a thread with axial:longitudinal pitch Y, wherein pitch Y is greater than pitch X, such that axial rotation of the second external dose setting knob results in the same degree of axial rotation as the first knob, but greater longitudinal travel of the second external dose setting knob compared to the first knob.

[034] In certain embodiments of injection devices according to the present invention, the driving spring is positioned between the plunger and the proximal end of the actuation mechanism housing.

In other embodiments the driving spring may be offset compared to the plunger and biases the plunger indirectly.

[035] In certain specific embodiments, an injection device according to the present invention is for intravitreal injection and comprises a sheath enshrouding at least a distal portion of a needle assembly in fluid communication with said formulation chamber, the sheath being either an integral part of said sleeve or being adapted to engage the distal end of the sleeve and being adapted to slide between the elongated housing and the formulation chamber, and wherein the sheath is at least proximally slidable with respect to the needle so as to unsheath the needle during insertion of the needle into a subject and so as to push the sleeve, resulting in proximal movement of the sleeve against the restrainer and movement of the restrainer to a retention arm or toggle-releasing position, wherein the sheath has a distal eye-contacting surface.

[036] In certain aspects the eye-contacting surface has an outer perimeter that defines a circle or modified circle, said surface being annular or in the form of a perforated concave disc, discoid or 3-dimensional annulus surface, with the needle defining the centre of said circle, although other shapes may be used. Where the eye-contacting surface is annular or in the form of a perforated concave disc, discoid or 3-dimensional annulus surface, the diameter of the circle may be between 4 to 10 mm, more preferably between 6mm and 8mm, so as to provide a ready measurement of 2-5, preferably 3-4mm from the limbus to the pars plana, to ensure injection in the vitreous body of the eye. Where other eye-contacting surface shapes are used, this should still provide at least one eye-surface contacting edge that is 2-5mm, preferably 3-4mm from the needle to allow for correct positioning of the needle for intravitreal injection.

[037] In certain aspects the sheath has an external pad which is substantially coterminous with the eye-contacting surface for applying pressure next to the injection site after injection. The external pad may be a peripheral extension to the perimeter of the eye-contacting surface, or may extend from the external surface of the sheath.

[038] According to certain embodiments, injection devices according to the present invention may be for single use or for carrying out multiple injections, either of the same formulation or different formulations. Where the devices are for multiple injections, the needle hubs may be replaceable, the formulation chambers may be replaceable, or assembled elongated housings, complete with formulation chamber and needle assembly (typically also with a cap) may be replaceable. Where the devices are for single use, or the assembled actuation housing with formulation chamber is for single or limited multiple use, the formulation chamber may be integrally formed with the elongated

housing. Where the devices are for single use the needle may be integral with the elongated housing as well or it could be part of a separate replaceable needle assembly or hub. In certain aspects the elongated housing is adapted to receive pre-filled formulation chambers, where a needle assembly is integrally formed with the syringe body, or where the elongated housing is adapted to have a needle assembly or needle hub attached to it such that the needle is in fluid communication with the formulation chamber.

[039] According to another embodiment of the present invention there is provided a needle hub adapted to be attached to an injection device according to any of the above described injection device embodiments and comprising a needle and a body with the injection end of the needle protruding distally from it, the proximal end of the needle hub being adapted to connect to the engagement so that the needle can operatively communicate with the formulation chamber, the needle hub also including a sheath enshrouding the distal needle and main body, the proximal end of the sheath being operatively adapted, once the hub is connected to the injection device, to: retain the main body of the needle assembly within the sheath; to engage a sleeve of said injection device; and to fit and slide relative to the injection device. The body of the needle assembly may be integrally formed or overmoulded, or may be a separably or permanently attached component. The body may further have a proximal end having a proximal end of the needle protruding proximally from it and a main body with the injection end of the needle protruding distally from it, the proximal end of the body being adapted for engagement with the elongated housing or the formulation chamber, optionally via a snap, tight fit, screw or Luer lock mechanism. The needle hub may optionally also comprise a cap which fully enshrouds at least the distal end of said needle hub.

[040] According to an alternative needle hub embodiment, there is provided a needle hub for attachment to an injection device according to any of the above described injection device embodiments and comprising a main body having a proximal body and a distal body, the main body being either connected to a member adapted to engage the distal end of the elongated housing or formulation chamber or having a proximal end adapted to engage the distal end of the elongated housing or formulation chamber, the proximal body having a proximal needle extending proximally from it, the distal body comprising a distal needle extending distally from it, the proximal and distal bodies being adapted to connect together with a filter enclosed between them and between the two needles, the needle hub also comprising a sheath enshrouding the needle and main body, the proximal end of the sheath being adapted to: retain the main body of a needle assembly within the sheath when not in use; to engage the sleeve of said injection device; and to fit and slide within the elongated housing. Such an embodiment allows for avoidance of microparticulate matter that may

be present in the formulation in the formulation chamber and/or microparticulate matter that may arise as a result of the proximal needle piercing the distal seal on the formulation chamber. The proximal and distal needles may be of the same gauge (outer diameter) or may be different, with the proximal needle having a greater or smaller gauge than the distal needle. However, because the proximal needle is not involved in the injection, and is therefore not the subject of limitations for comfortable intravitreal injection, it may be of any desired gauge, whereas where the needle hub is for intravitreal injection, the distal needle may preferably be no larger than gauge 25 (approx. 0.5mm outer diameter) or finer, preferably gauge 27 (approx. 0.4mm outer diameter) or finer. The needle hub may optionally also comprise a cap which fully enshrouds at least the distal end of said needle hub, and typically will comprise such a cap when distributed. Optionally the cap also includes means to ensure that the cap does not rotate axially with respect to said main body when connecting the needle hub to said injection device.

[041] According to certain aspects the needle hub is for intravitreal injection and has a distal eye-contacting surface, as described earlier. In certain aspects the sheath is substantially cylindrical for most of its length, with a frustoconical distal end.

[042] The needle hub may comprise a sheath which has an external pad which is substantially coterminous with the eye-contacting surface for applying pressure next to the injection site after injection. The external pad may be a peripheral extension to the perimeter of the eye-contacting surface, or may extend from the external surface of the sheath.

[043] The sheath may also comprise features that inhibit axial rotation of the sheath relative to the cap while securing the needle hub to an injection device according to the present invention.

[044] According to another embodiment of the present invention there is provided a needle hub adapted to be attached to an injection device, the injection device including a formulation chamber and an engagement allowing connection to a formulation chamber, the needle hub comprising a needle and a body with the injection end of the needle protruding distally from it, the proximal end of the needle hub being adapted to connect to the engagement so that the needle can operatively communicate with the formulation chamber, the needle hub also including a sheath enshrouding the distal needle and main body, the proximal end of the sheath being operatively adapted, once the hub is connected to the injection device, to: retain the main body of the needle assembly within the sheath; to engage a sleeve of said injection device; and to fit and slide relative to the injection device, said needle hub optionally also comprising a cap which fully enshrouds at least the distal end of said needle hub.

[045] According to another embodiment of the present invention there is provided an actuator mechanism for an injection device, the mechanism having a plunger, the distal end of the plunger being adapted to engaging a stopper, and the plunger being in communication with a driving spring which biases the plunger distally when the actuation mechanism is primed for injection, wherein the plunger is held in position against said stress by a retention arm or toggle having at least one first surface adapted to engage an opposed complementary second surface to hold said plunger in an unactuated position when the actuation mechanism is primed for injection, the first and second surfaces being held in an engaged position by a restrainer which translates from an unactuated position or configuration to an actuated position or configuration when triggered, thereby allowing uncoupling of the engagement between the first and second surfaces and release of the plunger to move distally.

[046] According to another embodiment of the present invention there is provided an elongated housing assembly for use with any one of the above described injection device embodiments and comprising proximal and distal ends and which defines an inner lumen between said proximal and distal ends which includes or is adapted to receive and hold a formulation chamber relative to said actuation mechanism, said formulation chamber also having corresponding proximal and distal ends, and having a stopper between its proximal and distal ends for retaining formulation in said formulation chamber, and wherein said elongated housing also comprises a sleeve which is at least proximally slidable between the elongated housing and the formulation chamber and is adapted to engage the restrainer of the actuation housing, and wherein insertion of a needle connected to the elongated housing into a subject results in the sleeve sliding proximally.

[047] According to another embodiment of the present invention there is provided a dose delivery mechanism for an injection device, the injection device comprising a body with a distal end which, operatively, has a needle assembly attached thereto and a proximal end comprising an actuation mechanism with a plunger with distal and proximal ends, the injection device further including a formulation chamber also with distal and proximal ends and including a stopper between its distal and proximal ends and formulation between the stopper and the distal end of the formulation chamber, wherein the distal end of the plunger is adapted to engage the stopper, and wherein said dose delivery mechanism is adjustably coupled to the proximal end of the plunger such that a distance between the dosing mechanism and the device body, and therefore an allowable travel distance of the plunger, can be set to a specified value to set a selected volume of formulation for delivery.

[048] According to another embodiment of the present invention there is provided a method for operating an injection device, the injection device having an elongated housing having a proximal end and a distal end, the proximal end having an actuation mechanism and the distal end having or being adapted to have a needle attached thereto, the injection device further including a formulation chamber including a stopper; the actuation mechanism including a plunger, the distal end of the plunger being adapted to engage the stopper, the plunger being biased towards the distal end when the actuation mechanism is primed for injection, the plunger being held in position against the bias by a retention arm or toggle, so as to hold the plunger in an unactuated position when the actuation mechanism is primed for injection, the plunger being held in an engaged position by a restrainer which is adapted to translate from an unactuated position or configuration to an actuated position or configuration when triggered; the method comprising bringing the device into an operative position; triggering the restrainer to release the plunger from the engaged position, the plunger then moving distally to deliver formulation from the formulation chamber.

[049] Accordingly, suitable implementations of the present invention provide one or more of reduced trigger force, more accurate injection depth, accurate and adjustable dosing, protection of the needle and/or fluidic pathway of the device, including pre-injection priming and post-injection locked needle protection, correct positioning of injection (for intravitreal injection), dose delivery confirmation, use of pre-filled syringes or cartridges, automatic priming, or any combination thereof.

Brief Description of the Drawings

[050] Illustrative implementations of the present invention will be described with reference to the accompanying figures, in which:

[051] **Figure 1** shows an exploded view of the components of an injection device according to a first embodiment of the invention.

[052] **Figure 2** shows a longitudinal cross section of the exploded view shown in Figure 1.

[053] **Figure 3** shows a side view of an injection device according to a first embodiment of the invention with a screw plug in place of a needle hub (which may be provided separately).

[054] **Figure 4** shows a longitudinal cross section of the device as illustrated in Figure 3.

[055] **Figure 5** shows a side view of an injection device according to a first embodiment of the invention with a needle hub installed, the needle hub also comprising a needle sheath with *pars plana* measuring rim and protective cap substantially enshrouding the sheath and needle.

[056] Figure 6 shows a longitudinal cross-section of the device as illustrated in Figure 5.

[057] Figure 7 shows longitudinal cross-sectional details of an actuation mechanism according to a first embodiment of the present invention, as well as its interaction with the remainder of the injection device.

[058] Figure 8 shows longitudinal cross-sectional details of the distal end of an injection device according to an embodiment of the invention, including an attachable/detachable needle hub (with sheath and covering cap) and its interaction with the remainder of the injection device.

[059] Figures 9 to 11 show longitudinal cross-sectional details and workings of an injection device according to a first embodiment of the present invention during an injection sequence (Figure 9: pressure just applied to proximal end of the injection device against a subject to be injected; Figure 10: injection depth achieved and plunger released; and Figure 11: pressure removed from proximal end and sheath returned and locked into needle-enshrouding position), with Figure 9 showing a longitudinal cross section which is longitudinally turned 90° compared to Figures 10 and 11.

[060] Figure 12 shows close-up longitudinal cross-sectional details of the proximal end of the device as shown in Figure 11, at a slightly different angle to show details.

[061] Figure 13 shows external details of the actuation mechanism housing according to a first embodiment of the invention.

[062] Figure 14 shows close-up longitudinal cross-sectional details of the proximal end of the device according to a first embodiment of the invention when primed for injection, showing details of the interaction between the main body and cap of the actuation mechanism housing as well as details of retention arms, restrainer and plunger when primed for injection.

[063] Figure 15 shows details of the distal end of a preferred, intravitreal injection embodiment according to the present invention.

[064] Figures 16 and 17 show details of the interaction of retention arms, the restrainer, the plunger and the driving spring when primed for injection (Figure 16) and once injection has been performed (and the plunger has been released).

[065] Figures 18 to 20 show different close-up angles of retention arms according to the present invention viewed.

[066] **Figure 21** shows an exploded view of the relevant components of an injection device according to a second embodiment of the invention, where those components include different components to the first embodiment illustrated in Figure 1.

[067] **Figure 22** shows a longitudinal cross section of the exploded view shown in Figure 21.

[068] **Figures 23 to 25** show longitudinal cross-sectional views of an injection device according to a second embodiment of the invention: Figure 23 shows such a view with a screw plug in place of a needle hub, which may be provided separately; Figure 24 shows such a view with a needle hub installed, the needle hub also comprising a needle sheath with *pars plana* measuring rim and pressure pad, and protective cap substantially enshrouding the sheath and needle; and Figure 25 shows the device of Figure 24 with the protective cap removed.

[069] **Figures 26 to 31** show longitudinal cross-sectional details and workings of an injection device according to a third embodiment of the present invention during an injection sequence. Figures 27 and 28: pressure just applied to proximal end of the injection device against a subject to be injected, with sleeve contacting restrainer, Figure 28 being at a slightly different angle to show details of physical interactions; Figure 29: injection depth achieved and plunger released; and Figures 30 and 31 pressure removed from proximal end and sheath returned and locked into needle-enshrouding position, Figure 31 being at a slightly different angle to show details of physical interactions.

[070] **Figure 32** shows an actuation mechanism housing according to a third embodiment of the invention.

[071] **Figure 33** shows an actuation mechanism housing proximal dose adjustment cap according to a third embodiment of the invention.

[072] **Figure 34** shows the proximal end of a plunger according to a third embodiment of the invention.

[073] **Figure 35** shows an exploded view of the components of an injection device according to a fourth embodiment of the invention.

[074] **Figure 36** shows a longitudinal cross section of the exploded view shown in Figure 35.

[075] **Figure 37** shows a longitudinal cross-sectional side view of an injection device according to a fourth embodiment of the invention with a screw plug in place of a needle hub, a longitudinal cross-section of the needle hub, showing its components, being illustrated underneath.

[076] **Figure 38** shows a longitudinal cross-sectional side view of an injection device according to a fourth embodiment of the invention with a needle hub installed, the needle hub also comprising a needle sheath with *pars plana* measuring eye-contacting surface and protective cap substantially enshrouding the sheath and needle. The cross-section shown is rotated along its longitudinal axis by 45° compared to Figure 37 and showing the sides of the sleeve leaves, whereas Figure 37 shows longitudinal 'ribs' extending internally beyond the sleeve leaves to engage the formulation chamber and hold it in place.

[077] **Figure 39** shows another longitudinal cross-sectional side view of an injection device as illustrated in Figure 38, but rotated along its longitudinal axis by 90° compared to Figure 38.

[078] **Figure 40** shows a lateral plan view of an injection device as illustrated in Figures 37-39, but without protective sheath cap or proximal cap.

[079] **Figures 41 to 43** show longitudinal cross-sectional details and workings of an injection device according to a fourth embodiment of the present invention during an injection sequence (Figure 41: pressure applied to proximal end of the injection device against a subject to be injected, with injection depth achieved and dose about to be released; Figure 42: dose delivered; and Figure 43: pressure removed from proximal end and sheath returned and locked into needle-enshrouding position).

[080] **Figures 44 to 46** show details of the interaction of retention arm, the sleeve/restrainer, and the plunger during an injection sequence (Figure 44: actuation mechanism primed for injection, with retention arm and sleeve/restrainer in drive member-restraining position; Figure 45: actuation mechanism triggered, with retention arm and sleeve/restrainer in drive member-releasing position; Figure 46: pressure removed from proximal end and sleeve returned to its distal position, with retention arm fully deflected outwards, locking the sleeve and sheath in distal, needle-enshrouding position).

[081] **Figure 47** is a transparency showing the actuation housing and its interaction with the retention arm, the driving spring, and plunger.

[082] Figure 48 is a transparency showing the actuation housing and its interaction with the retention arm, the first spring, and plunger with sleeve/restrainer and sleeve spring in plunger-retaining position.

[083] Figure 49 is a transparency showing the actuation housing and its interaction with the retention arm, the driving spring, plunger, sleeve/restrainer and sleeve spring in plunger-retaining position, and proximal cap positioned on top of the actuation housing.

[084] Figure 50 shows details of a preferred sleeve/restrainer according to the invention.

[085] Figure 51 shows two views of details of an embodiment of a retention arm according to the invention.

[086] Figures 52 to 56 show details of the interaction of retention arm, the plunger, the proximal cap and the actuation housing during a priming, '0' calibration, dose setting and 'dose delivered' sequence (Figure 52: injection device assembled, but without needle in place, with formulation chamber under stress; Figure 53: formulation chamber seal perforated by needle, releasing some stress on formulation chamber and allowing proximal cap to come to rest on complementary surface of actuation housing; Figure 54: proximal cap turned to release remaining stress on formulation chamber, and bringing retention arm retaining ledge and complementary plunger ridge into engagement, and thereby 'zeroing' the dosing system – proximal cap still resting on complementary surface of actuation housing; Figure 55: proximal cap further rotated and lifting proximally off complementary surface of actuation housing thereby allowing dose setting as determined by distance proximal cap is lifted off complementary surface of actuation housing; Figure 56: dose delivered, with proximal cap returning to rest on complementary surface of actuation housing).

[087] Figures 57 and 58 show details of a preferred actuation housing according to the invention, Figure 57 providing a side plan view and Figure 58 providing a view into the inside of the actuation housing as viewed from the distal end.

[088] Figure 59 shows details of the insides of a preferred proximal cap according to the invention as viewed from the distal end.

[089] Figure 60 shows details of the interactions between the actuation housing, proximal cap and plunger.

[090] Figure 61 shows an exploded view of the components of an injection device according to a fifth embodiment of the invention.

[091] **Figure 62** shows a longitudinal cross section of the exploded view shown in Figure 61.

[092] **Figures 63 to 69** show longitudinal cross-sectional details and workings of an injection device according to a fifth embodiment of the present invention during priming (Figures 63 to 65), dose setting (Figure 66) and injection (Figure 67: pressure applied to distal end of the injection device against a subject to be injected, with injection depth achieved and dose being delivered; Figure 68: dose delivered; and Figure 69: pressure removed from proximal end and sheath returned and locked into needle-enshrouding position).

[093] **Figure 70** shows a longitudinal cross-sectional side view of the four main components of an injection device according to a fifth embodiment of the invention comprising: an actuation mechanism **20d** and components; formulation cartridge **240** and components; elongated housing **10d** and components; and needle hub **150d** and components.

[094] **Figure 71** shows an exploded view of actuation mechanism **20d** (as shown in Figure 70) and components.

[095] **Figures 72 to 76** show details of restrainer **130d**, retention toggle **120d**, plunger (plunger) **80d** according to a fifth embodiment of the invention and their interaction/connections.

[096] **Figures 77 to 79** show details of the interaction of retention toggle **120d**, sleeve leaves **76d**, restrainer **130d**, and plunger **80d** during an injection sequence (Figure 77: actuation mechanism primed for injection, with retention toggle, sleeve and restrainer in plunger-retaining position; Figure 78: actuation mechanism about to be triggered, with sleeve and restrainer only just in drive member-releasing position; Figure 79: actuation mechanism triggered, with toggle rotated about axis **121d** and sleeve and restrainer in drive member-release position).

[097] **Figures 80 to 82** show external and internal details of an actuation housing **110d** according to a fifth embodiment of the present invention.

[098] **Figures 83 and 84** show external and internal details of a proximal cap **290d** according to a fifth embodiment of the present invention.

[099] **Figure 85** shows an exploded view of elongated housing **10d** (as shown in Figure 70) and components.

[100] **Figures 86 and 87** show external and internal details of an elongated housing **10d** according to a fifth embodiment of the present invention.

[101] **Figures 88 and 89** show external and internal details of a sleeve **70d** according to a fifth embodiment of the present invention.

[102] **Figures 90 and 91** show external and internal details of a cartridge centering/ spring retaining plug **440** according to a fifth embodiment of the present invention.

[103] **Figure 92** shows a longitudinal cross-sectional side view of an elongated housing **10d** according to a fifth embodiment of the present invention (as shown in Figure 70), showing its components and their relative positioning.

[104] **Figures 93 to 95** show details of a needle hub according to another specific embodiment of the present invention.

[105] **Figures 96 and 97** show details of another specific embodiment of a dose-setting mechanism according to the present invention: Figure 96A – external details; Figure 96B longitudinal cross-section showing internal details; Figure 97 partial cut-away section showing further details.

[106] **Figure 98** show details of an alternative dose-setting mechanism according to an embodiment of the present invention.

[107] **Figures 99 and 100** shows details of a self-setting retention arm mechanism according to an embodiment of the present invention.

[108] **Figures 101 and 102** show details of a camming retention arm (not requiring a biasing spring for operation) and its operation.

[109] **Figures 103 to 107** show details of alternative plunger driving mechanisms for use in various embodiments according to the present invention.

[110] **Figure 108** show details of the use of a multi-use injection device with replacement of elongated housing (complete with needle assembly and formulation chamber) according to an embodiment of the present invention.

Definitions

[111] As used herein, the term "adaxial" means towards or facing an axis. The term "abaxial" means away from or facing away from an axis.

[112] As used herein, the term "distal" means the end or direction of injection. The term "proximal" means the end or direction toward the rear of the injector or toward the rear of the injection member and/or injector and/or injection member.

[113] As used herein, the term "engage" means that two or more items interact such that one item acts on one or more other items with which it 'engages' and the items that 'engage' may connect with one another or may simply make contact with one another. Corresponding terms such as "engages", "engaged" and "engagement" are intended to have corresponding meanings.

Detailed Description

[114] The present invention will now be described by way of reference to various specific embodiments exemplifying the invention which is, however, not to be so limited, as various modifications may be made to the specific embodiments described herein without departing from the inventive concept illustrated by them. It will in particular be understood that the various embodiments are intended to be illustrative and not limitative. In particular, it will be understood that the disclosure encompasses the substitution of equivalent mechanical structures, for example kinematic inversions, alternative bias means, and variations in geometry and materials. It will also be appreciated that devices intended for different volumes or for injectable materials of different viscosity or consistency may require corresponding adaptations to the device structures and dimensions.

[115] Having reference to Figures 1 to 6, a first embodiment of an injection device according to the present invention comprises a substantially hollow elongated housing **10** having proximal and distal ends, with an actuation mechanism **20** engaged at its proximal end, the actuation mechanism **20** comprising an actuation housing defined by proximal cap **100** and distal body portion **110**. The elongated housing **10** comprises internally extending longitudinal ribs **12** which define an inner lumen **30** adapted to receive and secure a formulation chamber **40** containing, or adapted to contain an active agent for injection into a subject and the formulation chamber also comprises corresponding proximal and distal ends. Stopper **50** is provided at least at the proximal portion of chamber **40** for retaining active agent therein. The distal end includes, or is adapted to be in fluid communication with, a needle **60**. The elongated housing also includes a sleeve **70** with leaves **74** which are positioned between the ribs, so that sleeve **70** is at least proximally slidable with respect to elongated housing **10**.

[116] In certain embodiments proximal cap **100** may engage with body portion **110** via complementary screw threads **105** and **118** on proximal cap **100** and body portion **110** respectively,

allowing for adjustment of driving member or plunger **80** (and stopper **50**) relative to formulation barrel **42**, and therefore for priming of needle **60** and adjustment of dosage to be delivered.

[117] Elongated housing **10**, actuation housing components **100** and **110** and sleeve **70** can comprise any suitable material as used in the art, including suitable polymeric materials, metals and/or metal alloys. In certain aspects, elongated housing **10**, actuation housing components **100** and **110** and sleeve **70** may be constructed of a polymeric material known to one having ordinary skill in the art, including but not limited to polycarbonate ('PC'), acrylonitrile, butadiene, and styrene ('ABS') blends, polyethylene, polystyrene, or polyvinyl chloride. Such material may be manufactured into the aforementioned components by suitable means known to one having skill in the art, such as moulding.

[118] Each of the elongated housing **10**, sleeve **70**, proximal cap **100**, and body portion **110** may conveniently have at least internal profiles that are hollow cylindrical (optionally with two or more stepped inner diameters, and having additional features as described further below), especially elongated housing **10** and sleeve **70**, given the cylindrical profile of commercially available formulation chambers. However, external profiles are not necessarily so limited, and may include shaping that makes the injection device more ergonomic or easier to manufacture or package, and even the inner profiles may be other than cylindrical, although this may come with manufacturing, ease of assembly and/or functionality complications.

[119] In the specific embodiment illustrated in figures 1 to 14 sleeve **70** comprises a hollow cylindrical proximal body **72** which is housed within the actuation housing defined by proximal cap **100** and distal body portion **110**, with sleeve leaves **74** extending distally from body **72**, through corresponding slots in baseplate **112** of housing body portion **110** and into lumen **30** of elongated housing **10**. One or more sleeve leaves **74** may be omitted or comprise a window **76** which omission or window may coincide with a window **18** in elongated housing **10** such that the contents of formulation chamber **40** (if installed) can be viewed. In an alternate embodiment, the body of the elongated housing or other components may be composed of materials which are transparent or translucent, thus facilitating viewing of the contents of the formulation chamber or other internal components.

[120] Elongated housing **10** and actuation mechanism **20** may engage with one another by any suitable means, such as those known in the art, which will ensure that in use they remain in a fixed positional relationship relative to one another. For example, the mutually compatible surfaces may be welded, crimped, snapped, screwed or glued together.

[121] According to an embodiment, actuation mechanism **20** may comprise a driving member or plunger **80** the distal end of which engages with, or is adapted to engage with stopper **50** of the formulation chamber. As well as interlock, overlap, screw into or onto, amongst others, 'engage' and corresponding terms may include mere pushing against, such that plunger **80** may be adapted to simply come up against and push stopper **50**. At its proximal end plunger **80** engages with actuation mechanism housing cap **110**, with at least one driving spring **90** positioned between cap **100** and plunger **80**. Plunger **80** may comprise any suitable means for holding driving spring **90** between plunger **80** and cap **100**, such as spring retaining cup or ridge **82** shown in Figures 1, 2, 4 and 6 (as well as Figures 7, 9-12, 16 and 17) formed close to the proximal end of plunger **80**.

[122] Having reference to figures 4, 6, 7, 9-12, 14, 16 and 17, when an injection device according to the present invention is put together, with formulation chamber **40** in place and plunger **80** engaged with stopper **50**, and the device is primed for injection, driving spring **90** is held under stress with plunger **80** held in position by retention arm **120**. To best control retention arm release force (i.e., force that needs to be applied against a surface, such as the eye, in order to actuate the injection device), a retention arm **120** is provided with outwards bias (i.e., away from plunger **80**), with retention arm being held in plunger engaging position against the bias by a restrainer **130** which is at least proximally slidable, restrainer **130** being in restraining position when distal (figures 4, 6, 7, 9, 14 and 16) and in releasing position when proximal (figures 10, 11, 12 and 17). In use, restrainer **130** is driven proximally by sleeve **70** when sleeve **70** is slid proximally relative to elongated housing **10** by applying distal pressure on the injection device against a surface to be injected, thereby releasing retention arm **120** to deflect away from plunger **80**, allowing driving spring **90** to drive plunger **80** and stopper **50** distally.

[123] Having reference to figures 12, 14, 16-20, 41-47 and 51, preferred forms of retention arm **120**, **120c** and restrainer **130** and **130c** are illustrated although once given the benefit of this disclosure other suitable means/configurations will be readily apparent to those skilled in this area, and the invention is not to be seen as being limited to the particular preferred forms of retention arm or toggle and restrainer illustrated. Alternative retention arms or toggles and complementary restrainers may, for example, comprise different configurations and/or single or three or more retention arms/toggles held against their bias by similar restrainers such as restrainer **130** as illustrated, or one or more different means, other than a shaped disc as illustrated.

[124] Having reference to the retention arm **120** as illustrated in figures 12, 14, and 16-20, each comprises an extended 'arm' with a pivot/fulcrum point **121** at the proximal end (like a shoulder) adapted to engage a pin or axle **140** (shoulder joint) provided at the proximal end of proximal cap

100. Alternatively, pin(s) or axle(s) **140** may be formed separately or even form part of retention arm **120** and engage with proximal cap **100**, or corresponding part of the actuation mechanism housing via corresponding joints or fulcrum points. In one embodiment, in the 'armpit' portion of retention arm **120**, adaxially situated is a spring arm **123** (which may be formed integrally with retention arm **120** or separately, and may be made of a stiff, elastomeric or springy material, which may be the same or a different material than the rest of retention arm **120**) with corresponding recess **124**. In an alternative embodiment a spring or spring arm may be attached to the side of plunger **80**, or even be an integral part of plunger **80**, and push against retention arm **120**, in certain embodiments against a surface of retention arm **120** corresponding with recess **124**. Moving distally along the 'arm' of retention arm **120** is a step in or axially oriented 'elbow' forming an inwardly directed ledge **125** which, when in plunger-engaging and retaining position, is substantially perpendicular to the axis of plunger **80** and adapted to engage an opposed ridge or ledge **86** formed on plunger **80**, and which may conveniently be the lower, outer edge of spring retaining cup **82**. Retention arm **120** extends distally beyond inwardly directed ledge **125** (thus forming the equivalent of a 'forearm' in the 'arm' analogy), ending with a 'hand' comprising a concave flange **127** adapted to rest against the shaft of plunger **80**, concave flange **127** having further flanges or tabs (retention tabs) **128** extending outwardly either side of it, one of retention tabs **128** (the right hand side one, looking from the adaxial side, in this example) having a further distally extending flange/tab **129** ('sheath locking tab'). Retention arm **120** may be made of any suitable material as used in the art, including suitable polymeric materials, metals and/or metal alloys and, as mentioned above, may be made of a combination of any such materials. Where spring arm **123** is an integral part of the whole retention arm **120**, retention arm **120** may be made of a suitable firm, elastomeric polymeric material such as polycarbonate, polyoxymethylene, nylon and the like. Triggering pressure (i.e., the amount of proximally directed force that needs to be applied by sleeve **70** against restrainer **130**, and therefore distal force that needs to be applied against a surface to be injected) using such a retention arm is proportional to the ratio a:b between the distance "a" between pivot point **121** and the proximal surface of tab **128** and the adaxial extension distance "b" of the edge of ledge **125** compared to pivot point **121**, so for a given bias strength provided by spring arm **123**, the longer "a" is, or the smaller "b" is, the smaller the force required to trigger the device, allowing for less discomfort to a subject being injected. Therefore, importantly for certain applications such as intraocular injections, the triggering pressure can be adjusted through adjustment of the ratio a:b in this particular embodiment, and through adjustment of equivalent mechanical advantage ratios for other injection device embodiments described below.

[125] Having reference to the restrainer **130** as illustrated, this is provided as a flat disc which may be any suitable thickness, but typically from about 2mm to about 50mm, typically from about 5mm to about 20mm, and may be made of any suitable material as used in the art, including suitable polymeric materials, metals and/or metal alloys. Having reference to Figures 16 and 17, in one embodiment restrainer **130** may have suitable spaces cut into it: i) opposed retaining channels **133** to hold the opposed pairs of retention tabs **128** to hold the pair of retention arm **120** against plunger **80** and against bias generated by compression of spring arm **123** into recess **124** when in a retaining position; ii) releasing channel **136** to provide space for retention arm to deflect away from plunger **80** when restrainer **130** is slid proximally to release retention tabs **128**; and iii) space created at the cross-section of opposed retaining channels **133** and releasing channels **136** to allow restrainer **130** to fit over plunger **80** and move freely along at least that part of plunger **80** engaged by the lower portion of retention arm **120** (below ledge **125**).

[126] The embodiment illustrated in figures 1-12 is adapted to utilise a pre-filled needleless formulation chamber **40**, which may optionally be vacuum or voidless filled, and to have a separately provided needle hub **150** attached, via any suitable mechanism known in the art, such as tight fit, snap, Luer lock, bayonet or screw mechanisms. However, formulation chambers, pre-filled or not, with integral or otherwise attached needles may also be employed, as described below. In the embodiment illustrated in figures 1-12, and with particular reference to figures 1-4, pre-filled formulation chamber **40** as may, for example, be provided separately or form an integral part of the injection device as provided, comprises a cylindrical barrel **42** (which may be made of glass or a suitable polymeric material, optionally silanized or siliconized) with seal **44** and barrel connector **46** (which may be formed integrally with barrel **42**, if made of polymeric material, or may be formed separately and be attached to the distal end of barrel **42**, such as by gluing, snapping, crimping or other suitable means), as well as a stopper **50**, with formulation comprising active agent being contained within barrel **43** between seal **46** and stopper **50**. Pre-filled needleless formulation chambers such as illustrated in figures 1-12 also have a barrel flange at the proximal end of barrel **42** projecting axially outwards and typically used for providing purchase for a forefinger and middle finger for holding the syringe while applying pressure on the proximal end of a plunger, to perform injection. However, in the embodiment illustrated in figures 1-12, and especially as illustrated in figures 7-12, according to one embodiment formulation chamber **40** may be retained in the injection device in the lumen formed by elongated housing **10**, with barrel flange **49** at the proximal end of barrel **42** sitting in a recess **15** formed in the proximal end of elongated housing **10** and which, together with baseplate **112** of actuation housing distal body portion **110**, secures formulation chamber **40** in position within the injection device. A close fit of formulation chamber **40** within

elongated housing **10** provides further rigidity to the retention of formulation chamber **40** within the injection device. Typically a pre-filled formulation chamber **40** will be provided a syringe cap **48** screwed into barrel connector **46** to ensure sterility and cleanliness within the barrel connector until syringe cap **48** is removed prior to attachment of needle hub **150**. In other embodiments plunger **80** may assist in holding formulation chamber **40** in place by applying pressure against stopper **50**.

[127] In the embodiment described immediately above, and with reference to figures 1, 2 and 8, a needle hub **150** may comprise a needle **60** extending from both sides of an overmoulded body **160** having a proximal connector end **164** adapted to engage and connect with barrel connector **46** and having a shorter end of needle **60** extending proximally therefrom sufficiently to pierce seal **44** when hub **150** is fully connected with barrel connector **46**, and a main substantially cylindrical body **168** adapted to fit closely, but slidably within sheath **170** which has a proximal end **175** adapted to clip around body **168** thereby retaining body **168** within sheath **170**, but with connector end **164** protruding proximally from sheath **170**. In an alternative embodiment needle hub **150** is made in two parts, each part with an over moulded needle (a proximal needle to pierce seal **44** or **246**, and a distal needle for performing the injection) which are then joined together (needles pointing in opposing directions) with a filter between them. This would be so that any particles that may be generated in piercing the prefilled cartridge or prefilled syringe, or even any microparticulate matter present in the formulation are filtered out. Proximal end **175** is also adapted to engage sleeve **70** when hub **150** is fully connected with barrel connector **46**. When not in use, hub **150** (whether attached to connector **46** or not) may comprise a cap **180** ideally adapted to clip onto sheath **170**. In certain embodiments cap **180** may comprise a guide **185** for securing and protecting needle **60** within the needle hub. Alternatively, or in addition, the distal end or surface **173** of sheath **170** may comprise a guide for securing and protecting needle **60** within the needle hub. Having reference to at least figures 1, 2 and 15, distal surface **173** of sheath **170** may act as the surface for contacting a subject, or body part thereof, for injection. Such a contacting surface of said sheath may, in further embodiments, comprise a pad **177** made of softer and/or spongier and/or adherent material than sheath **170**, such as silicone or rubber or an absorbent material. In further embodiments such distal surface **173** of sheath **170** may be provided with features such as protrusions, ridges and/or other textural elements. In yet further embodiments, the contacting surface of the distal surface of sheath may include a combination of the aforementioned features or materials. Such materials and features may assist in holding the distal surface in position (for example in the correct injection position on the eye surface for intraocular injection) during the injection procedure, and may further assist the clinician in controlling or retaining the position of the eye in a desirable position during the injection. Although not shown, needle hub **150** may comprise a biasing means, such as a spring, within sheath

170, which urges sheath **170** distally with respect to body **168** and therefore needle **60**, to keep needle **60** sheathed when not in use. Sheath **170** may be substantially hollow cylindrical for all or most of its length, although other shapes may be contemplated. In certain embodiments sheath **170** may have a frustoconical distal end. Where sheath **170** and corresponding cap **180** are substantially cylindrical in shape, sheath **170** or cap **180** may comprise means to avoid axial rotation of cap **180** relative to sheath **170**, to allow use of rotational pressure on cap **180** to engage needle hub **150** with barrel connector **46**. Such means may, for example, comprise complementary longitudinal (i.e., distal-proximal extending) ridges and grooves, or introduction of some form of asymmetry in sheath **170** and cap **180** sufficient to stop axial rotation of cap **180** relative to sheath **170**. Further alternative means may, for example, comprise: a pin or stiff material slip that passes through corresponding holes formed in sheath **170** and cap **180**; or ribs extending from hub body **168** through corresponding slits in sheath **170** and engaging with corresponding slots in cap **180**. In certain aspects cap **180** is adapted to holding the remaining components of needle hub **150** rigidly in place relative to each other to enable handling and attachment of the hub to barrel connector **46**, such adaptations including, for example, clippable flanges, interacting complementary fins and slots or grooves and ridges, biasing means, and the like. In certain aspects cap **180** may be closed and have a distal internal void large enough to take a priming volume or dose adjust volume of formulation and the void may also have an absorbent pad to absorb that volume.

[128] Instead of a needleless formulation chamber **40** as per the embodiment illustrated in figures 1-12, a formulation chamber with needle (integral with barrel or not) may also be used. In such an embodiment there would be no need for a needle hub. However, in certain embodiments a sheath may be provided as an extension of sleeve **70**, and this may comprise a cap covering the end of the injection device when not in use.

[129] Readily available formulation chambers also include replaceable or disposable cartridges, which typically are not provided with barrel connectors but, instead, comprise a barrel with a seal at the distal end that is held in position by a crimped ring, or similar, a stopper towards the proximal end, and no barrel flange. Having reference to figures 21 to 25, a second embodiment of injection devices according to the present invention is provided which encompasses the use of such replaceable or disposable cartridges, which involves a change in the configuration of elongated housing **10**, and figures 21 to 25 provide the details of those changes. In particular, because replaceable or disposable cartridges do not have a barrel connector, according to the present embodiment a needle hub connector **210** is provided as an internally threaded collar supported by radially intruding extensions **220** of elongated housing **10b**. Radially intruding extensions **220**

provide slots between them, corresponding with equivalent slots in base plate **112** of body portion **110**, for sleeve leaves **74** to move within, allowing for the use of the same sleeve **70** as described above. The proximal end of needle hub connector **210** provides a recessed seat **230** for accommodating the distal end of replaceable or disposable cartridge **240** (comprising barrel **243** which may be made of glass, optionally silanized, or a suitable polymeric material, optionally siliconized, seal **246**, typically but not necessarily made of synthetic rubber, such as butyl rubber, and crimped ring **248**, typically but not necessarily made of aluminium, which holds seal **246** in place against the distal rim of barrel **243**). Between recessed seat **230** and hub connector **210** is a channel **250** allowing for the proximal end of needle **60** to pass through from connector hub **210**, through seal **246** and into the lumen of barrel **243**. In one embodiment, in order to secure replaceable or disposable cartridge **240** into position within elongated housing **10b**, the body portion of the actuation housing may be modified to provide body portion **110b** having a modified base plate **112b** comprising a distally extending collar **119** which surrounds plunger **80** and extends into the lumen within elongated housing **10b** and sleeve **70**, said collar extending into said lumen the correct distance to ensure that replaceable or disposable cartridge **240** is secured in said lumen such that it is substantially immobilised therein. Having reference to figures 23 to 25, needle hub **150**, syringe cap **48**, as well as the remainder of actuation mechanism **20** (other than body portion **110b**) can be the same as, or similar to those as already described above, and as shown in Figure 22, elongated housing **10b** may include the option of a window **18b** which coincides with a window **76** in sleeve leaf **74**, such that the contents of replaceable or disposable cartridge **240** (if installed) can be viewed.

[130] Having described the main components of certain injection devices according to the present invention, its mechanics during use will now be described.

[131] Firstly, and with reference to figures 1 to 20, the device may be provided as a single-use, pre-packaged sterile device ready for injection, or it may be provided without formulation chamber, either embodiment optionally without needle hub **150** (provided separately in a sterilised packaged form). If a formulation chamber **40** is provided separately, ideally pre-filled, actuation mechanism **20** with sleeve **70** is separated from elongated housing **10** and formulation chamber **40** is inserted into elongated housing **10** with barrel flange **49** seated into recess **15**. Sleeve leaves **74** are then positioned around barrel **42** and elongated housing **10** and actuation mechanism **20** are brought together and fixed in position, at the same time engaging the distal end of plunger **80** with stopper **50**. A needle hub **150** is then connected to barrel connector **46** (if not already connected, or if a formulation chamber with integral needle hub is not being used), with plug **48** being removed first.

If the formulation chamber is vacuum filled, this assembly will result in positive pressure within formulation chamber **40** and, once the proximal end of needle **60** pierces seal **44** the positive pressure within formulation chamber **40** will result in expulsion of formulation from barrel **42** into needle **60**, resulting in a self-priming system.

[132] Once the injector is assembled, restrainer **130** will be in its distal, restraining position, with opposed pairs of retention tabs **128** of retention arm **120** held substantially together in retaining channels **133** (against abaxial bias resulting from compression of spring arms **123** into recesses **124**), and substantially against plunger **80**, with inwardly directed ledge **125** engaging with opposed ridge/ledge **86** of plunger **80**, thereby holding the plunger in 'primed' position against bias provided by driving spring **90**.

[133] If the system is not self-priming, according to one embodiment the system may be primed by adjusting the position of proximal cap **100** relative to body portion **110** by screwing proximal cap **100** into body portion **110** sufficiently to prime needle **60**. In certain embodiments the dosage to be delivered during injection may also be controlled by adjusting position of proximal cap **100** relative to body portion **110** and therefore the travel distance of plunger **80** during injection.

[134] It will be appreciated that operation of both the self-priming mechanism, or the dosage adjustment by operation of cap **100**, cause a quantity of the supplied dosage in the formulation chamber to be expelled from the injection device.

[135] Once the system is primed, and dosage set if required, the distal surface of sheath **170** (or pad **170** if provided) is placed against the surface to which injection is to be made and pressure applied in a distal direction. This pressure results in sheath **170** sliding proximally into elongated housing **10** and against the distal ends of sleeve leaves **74** and corresponding proximal sliding of sleeve **70** up into the actuation housing defined by proximal cap **100** and distal body portion **110** and against bias provided by at least one sleeve spring **190** between the actuation housing and spring-engaging ridge or cup **78** on the outer circumferential edge of sleeve body **72**. As sleeve **70** moves proximally into the actuation housing its proximal surface engages the distal surface of restrainer **130**, pushing restrainer **130** proximally. Once restrainer **130** has moved the required distance proximally (as a result of needle **60** reaching the desired injection depth) retention tabs **128** are no longer held together and against plunger **80** in channels **133** and, as a result, the bias provided by spring arms **123** deflects the 'arms' of retention arm **120** away from plunger **80** and into the space provided by releasing channel **136** (with the abaxial deflection of the distal ends of retention arm **120** being limited by the inner wall of sleeve **70**), breaking the engagement of ledge **125** and

ridge/ledge **86** and releasing plunger **80** which, under pressure from first spring **90**, is driven distally, resulting in formulation being expelled from the distal end of needle **60**.

[136] In certain embodiments plunger **80** has a ridge **84** and base plate **112** of body portion **110** has a proximally extending collar surrounding a portion of the length of plunger **80** and providing an upper surface **115** and together, ridge **84** and surface **115** define the end travel of plunger **80** during injection, when ridge **84** reaches, and is stopped by surface **115**. This, especially together with adjustment of proximal cap **100** relative to body portion **110**, allows for a defined travel distance for plunger **80**, and therefore stopper **50**, during injection and therefore for a delivery of a defined dosage. In certain embodiments proximal cap **100** and/or body portion **110** may have dosage markings **200** calibrated for particular formulation chambers.

[137] Once injection has been performed, distally applied pressure is eased or removed and, as a result, sleeve spring **190**, applying pressure on ridge or cup **78** of sleeve **70**, which is no longer opposed, urges sleeve **70** distally, which in turn results in sheath **170** being urged distally to once again cover needle **60**. Also, as a result of sleeve **70** being urged distally, its inner wall no longer limits the further abaxial travel of retention arm **120**, which then deflects further abaxially towards the walls of body portion **110** of the actuation mechanism housing (and radially outward of pivot point **121**), with sheath locking tabs **129** then obstructing potential proximal travel of sleeve **70** and therefore of sheath **170**, thereby locking sheath **170** into a needle covering position, making the device safe (figures 11 and 12; see also figures 30 and 31). The proximal end of the sleeve may be adapted to better engage the sheath locking tabs/surfaces of the retention arm or toggle, and therefore more strongly lock the sleeve and thereby the sheath in a needle-covering position. Such adaptations may, for example, include notches in the sleeve, or even the proximal edge of the sleeve having flexible fingers, for engaging the sheath locking tabs or surfaces of the retention arm or toggle, although several other such means will be readily apparent to those skilled in this art.

[138] With reference to especially figures 12, 13, 16 and 17, a convenient adaptation of the injection devices according to the invention may be provided which allows sensing of the injection mechanism having been triggered. In particular, plunger **80** may comprise an extension **88** which extends proximally through a collar **107** at the proximal end of actuation housing cap **100**, and said extension moves/ recedes into cap **100** when the injection device is actuated, providing a signal that the device has in fact been actuated. Alternatively, extension **88** may comprise a ridge **89**, and collar **107** may comprise a thin flap, flaps or ridge **109** of suitably stiff, elastomeric or springy material (and may be formed integrally with cap **100** or separately, and may be made of the same or different material to cap **100**) extending adaxially to within the diameter of the abaxial extension of ridge **89**

and, when injection is performed, with plunger **80** being driven distally, ridge **89** is driven past flap, flaps or ridge **109** resulting in deflection of flap, flaps or ridge **109** in such a manner as to result in a noise, such as a 'click' signalling that the injection mechanism has been triggered.

[139] In a third embodiment of injection devices according to the present invention, an alternative configuration of the actuation mechanism to control the dose of formulation dispensed by the device during injection is provided. Referring to figures 26 to 34, compared to the previously described embodiments, the actuation mechanism housing is modified such that the actuation mechanism housing is defined by body portion **110b**, which comprises a proximal portion **260** and a distal portion **270**, wherein proximal portion **260** has a narrower diameter and inner bore than distal portion **270** and houses retention arm **120b** (which may be the same as retention arm **120** as previously described, and connected to the proximal end of proximal portion **260** via pins or axles **140b**, substantially as previously described) and restrainer **130b** is also slidably retained within proximal portion **260**. The inner bore of proximal portion **160** is slightly greater than the outer diameter of hollow cylindrical proximal body **72b** of sleeve **70b** such that hollow cylindrical proximal body **72b** may be slidably received by proximal portion **260** during the injection procedure and drive retaining member **130b** proximally. The interface of proximal portion **260** and distal portion **270** forms an outer ledge **273** and an inner ledge **276** that, with spring retaining ridge/cup **78b** holds sleeve spring **190b** in position in distal portion **270**. As well as modification of the actuation mechanism housing, plunger **80b** is also modified compared to plunger **80** previously described, having a threaded extension **280** that engages with a corresponding thread **293** in cap **290** which in turn fits slidably over proximal portion **260** of body portion **110b**. Plunger **80b** is otherwise substantially the same as plunger **80** previously described, including spring retaining cup **82b** and ridge/ledge **86b**. However, a ridge such as ridge **84** no longer has a role, as the travel distance of plunger **80b**, and therefore the amount of formulation dispensed during injection is now determined by the relationship between plunger **88b**, cap **290** and proximal portion **260** of body portion **110b**: once an injection device according to this embodiment is assembled, a desired dosage may be dialled up by screwing cap **290** proximally until the desired dosage marking **265** shows through window **296**. This lifts cap **290** proximally off ledge **273**, with the distance between the lower surface of cap **290** and ledge **273** defining the travel distance of plunger **80b**, and therefore volume of formulation dispensed during injection. When the actuation mechanism is triggered, as described earlier, the lower surface of cap **290** is driven to surface **275**, providing a convenient indicator that the device has been successfully triggered.

[140] Having reference to figures 35 to 60, a fourth embodiment of injection devices according to the present invention is provided which comprises a number of modifications compared to the third embodiment described above and, in particular, use of a single retention arm **120c** and restrainer **130c** being a proximal integral extension of sleeve **70c**. This embodiment also encompasses the use of replaceable or disposable cartridges.

[141] The injection device comprises a substantially hollow elongated housing **10c** having proximal and distal ends, with an actuation mechanism **20c** engaged at its proximal end, the actuation mechanism **20c** comprising an actuation housing **110c**. The elongated housing **10c** comprises internally extending longitudinal ribs **220c** which defines an inner lumen **30c** adapted to receive a formulation cartridge **240** containing, or adapted to contain an active agent for injection into a subject and the formulation chamber also comprises corresponding proximal and distal ends. Stopper **50** is provided at least at the proximal portion of cartridge **240** for retaining active agent therein. Because replaceable or disposable cartridges do not have a barrel connector, according to the present embodiment a needle hub connector **210c** is provided as an internally threaded collar supported by radially intruding ribs **220c** of elongated housing **10c**. Radially intruding extensions **220c** also provide slots for sleeve leaves **74c** to slide within. Compared to the earlier described embodiments, sleeve **70c** may comprise only two opposite sleeve leaves **74c** with opposed significant spaces between them, and elongated housing **10c** may include the option of a window **18c** which coincides with one of the opposed spaces (or two windows, each corresponding with one of the opposed spaces between the sleeve leaves **74c**), such that the contents of cartridge **240** (if installed) can be viewed. The proximal end of needle hub connector **210c** provides a radially intruding flanged surface upon which the distal end of cartridge **240** may be secured against by the force of plunger **80c** pushing against stopper **50**.

[142] In the embodiment illustrated in figures 35 to 60, actuation mechanism **20c** may comprise an actuation housing **110c**, proximal cap **290c**, the proximal portion of sleeve **70c**, including restrainer **130c** as an integral portion of sleeve **70c**, and plunger **80c**, the distal end of which engages with, or is adapted to engage with stopper **50** of the formulation cartridge. At its proximal end plunger **80c** is threaded and extends proximally beyond actuation housing **110c** through channel **263c** and engages with thread **293c** in proximal cap **290c**, with at least one driving spring **90** positioned between the proximal end of actuation housing **110c** and plunger **80c**. Plunger **80c** may comprise any suitable means for holding driving spring **90** between plunger **80c** and actuation housing **110c**, such as ridge **82/86c** shown in Figures 41, and 44 to 47 formed close to the proximal end of plunger **80c**. Actuation mechanism **20c** also comprises at least a sleeve spring **190c**, as well as

longitudinal ribs **330** extending internally from actuation housing **110c**, and adapted to engage the proximal end of spring **190c**, with the distal end of spring **190c** being engaged by the proximal portion of sleeve **70c**, such that spring **190c** is stressed between ribs **330** and sleeve **70c** thereby biasing sleeve **70c** towards a distal position.

[143] Proximal cap **290c** fits over actuation housing **110c** but is not fastened thereto, allowing for adjustment of proximal cap **290c** relative to plunger **80c** (and stopper **50**), and therefore for adjustment of dosage to be delivered.

[144] Elongated housing **10c** and actuation housing **110c** may engage with one another by any suitable means, such as those known in the art, which will ensure that in use they remain in a fixed positional relationship relative to one another. For example, the mutually compatible surfaces may be welded, pinned, crimped, snapped, screwed or glued together.

[145] In the specific embodiment illustrated in figures 35 to 60, and particularly Figure 50, sleeve **70c** comprises a hollow cylindrical proximal body **72c** with restrainer **130c** formed as an integral part of the proximal end of body **72c**, and which is housed within actuation housing **110c**, with two opposed sleeve leaves **74c** extending distally from body **72c**, through corresponding slots in the proximal end of elongated body portion **10c** and between ribs **220c** of elongated housing **10c**. The gaps between sleeve leaves **74c** may coincide with a window **18c** in elongated housing **10c** such that the contents of cartridge **240** (if installed) can be viewed. As described earlier, part or all of sleeve **70c** may optionally be constructed of a transparent material such that the contents of cartridge **240** may be viewed through window **18c** regardless. Sleeve **70c** may optionally also comprise surfaces **370** for engaging with retention arm **120c** for locking sleeve **70c** in a needle sheathing position, as described later, and/or a proximally extending arm for interacting with proximal cap **290c** to lock the injection device mechanism until a dosage is set for injection.

[146] Having reference to figures 37 to 43, when an injection device according to the present invention is put together, with cartridge **240** in place and plunger **80c** engaged with stopper **50**, with dose set and the device is primed for injection, driving spring **90** is held under stress with plunger **80c** held in position by retention arm **120c**, with retention arm being held in plunger-engaging position by restrainer **130c** which is an integral portion of sleeve **70c** and is at least proximally slidable, restrainer **130c** being in restraining position when distal (figures 39 and 44) and in releasing position when proximal (figures 42 and 45). In use, restrainer **130c** moves proximally (as part of sleeve **70**) when sleeve **70** is slid proximally relative to elongated housing **10c** by applying distal pressure on the injection device against a surface to be injected, thereby releasing retention arm

120c to deflect away from plunger **80c**, allowing driving spring **90** to drive plunger **80c** and stopper **50** distally.

[147] Having reference to figures 35-60, and particularly figures 39, 41-47, 50 and 51 and 57, retention arm **120c** and restrainer **130c** as used in the fourth embodiment are illustrated. In particular, retention arm or toggle **120c** as illustrated in figures 39, 41-47 and 51, comprise a single extended 'arm' with a pivot/fulcrum point **121c** at the proximal end (like a shoulder) adapted to engage a pin or axle **140c** (shoulder joint) provided at the proximal end of actuation housing **110c**. Alternatively, pin(s) or axle(s) **140c** may be formed separately or even form part of retention arm **120c** and engage with actuation housing **110c**, or corresponding part of the actuation mechanism housing via corresponding joints or fulcrum points **390**. Moving distally along the 'arm' of retention arm or toggle **120c** is a step in or axially oriented 'elbow' forming an inwardly directed ledge **125c** which, when in plunger-engaging and retaining position, is substantially perpendicular to the axis of plunger **80c** and adapted to engage an opposed ridge or ledge **82/86c** formed on plunger **80c**. Retention arm **120c** extends distally beyond inwardly directed ledge **125** (thus forming the equivalent of a 'forearm' in the 'arm' analogy), ending with a two-fingered 'hand' comprising a recess **127c** with flanges **128c** extending outwardly and distally either side of it and each having sleeve body engaging surfaces **129c** at their distal ends. Spring **360** (which may be made of a stiff, elastomeric or springy material, including steel) may be attached to the side of plunger **80c**, or even be an integral part of plunger **80c**, and push outwardly against a recess in the distal portion of retention arm **120c**. Triggering pressure (i.e.. the amount of proximally directed force that needs to be applied by sleeve **70c** against restrainer **130c**, and therefore distal force that needs to be applied against a surface to be injected) using such retention arm is proportional to the ratio a:b between the distance "a" between pivot point **121c** and the proximal surface of tab **128c** and the adaxial extension distance "b" of the edge of ledge **125c** compared to pivot point **121**, so for a given bias strength provided by spring **360**, the longer "a" is, or the smaller "b" is, the smaller the force required to trigger the device, allowing for less discomfort to a subject being injected.

[148] Having reference to the restrainer **130c** as illustrated, this is provided as an integral component of sleeve **70c** in the form of two flanges extending inwardly from the proximal end of sleeve body **72c**, with the two flanges being separated by a gap that allows the body of the 'arm' of retention arm **120c** to pass through, but not flanges **128c**, although other configurations will be readily apparent to those of skill in the art.

[149] With reference to figures 37 to 43, needle hub **150c**, which may be used with any of the second, third or fourth embodiments, may comprise a proximal body **168c1** overmoulded, glued or

otherwise attached to a needle **62** extending proximally from it and a distal body **168c2** overmoulded, glued or otherwise attached to a needle **64** extending distally from it, needle **62** being for piercing of the formulation chamber seal **246** and needle **64** being for insertion into a subject for injection. Proximal body **168c1** comprises a proximally formed connector end **164** (as previously described) adapted to engage and connect with barrel connector **210c**. Bodies **168c1** and **168c2** are adapted to connect together (and may, for example, be glued, welded, or otherwise coupled), with a filter **300** enclosed between the two bodies for filtration of any particles that may be generated in piercing the prefilled cartridge or prefilled syringe, or any microparticulate matter present in the formulation. Overall body **168c** is adapted to fit closely, but slidably within sheath **170c**. The proximal end of sheath **170c** is adapted to engage sleeve **70c** when hub **150c** is fully connected with barrel connector **210c**. When not in use, hub **150c** (whether attached to connector **210c** or not) may comprise a cap **180c** adapted to clip onto sheath **170c**. The distal end of sheath **170c** may comprise a guide **185c** for securing and protecting needle **64** within the needle hub and during injection. The distal end of sheath **170c** may comprise a pad **177c** made of softer and/or spongier and/or adherent material than sheath **170c**, such as silicone or rubber. Alternatively, the distal end of sheath **170c** may be provided with a rough or even spiky surface to assist in keeping the injection device in position during the injection procedure. (for example where reasonably accurate positioning is necessary, such as in the case of intravitreal injections). In further embodiments the distal surface of sheath **170c** may be provided with features such as protrusions, ridges and/or other textural elements. In yet further embodiments, the contacting surface of the distal surface of sheath may include a combination of the aforementioned features or materials. Such materials and features may assist in holding the distal surface in position (for example in the correct injection position on the eye surface for intraocular injection) during the injection procedure, and may further assist the clinician in controlling or retaining the position of the eye in a desirable position during the injection. Although not shown, needle hub **150c** may comprise a biasing means, such as a spring, within sheath **170c**, which urges sheath **170c** distally with respect to body **168c** and therefore needle **64**, to keep needle **64** sheathed when not in use. Sheath **170c** may be substantially hollow cylindrical for all or most of its length, although other shapes may be contemplated. In certain embodiments sheath **170c** may have a substantially frustoconical distal end. Where sheath **170c** and corresponding cap **180c** are substantially cylindrical in shape, sheath **170c** or cap **180c** may comprise means to avoid axial rotation of cap **180c** relative to sheath **170c**, to allow use of rotational pressure on cap **180c** to engage needle hub **150c** with barrel connector **210c**. Such means may, for example, comprise complementary longitudinal (i.e.. distal-proximal extending) ridges and grooves, or introduction of some form of asymmetry in sheath **170c** and cap **180c** sufficient to stop axial rotation of cap **180c**

relative to hub **150c**, such as previously described herein. As illustrated in figures 37 to 43 and particularly Figure 40, such means may comprise fins **340** extending from hub body **168c** through corresponding slits **350** in sheath **170c** and engaging with corresponding slots in cap **180c**. In certain aspects cap **180c** is adapted to holding the remaining components of needle hub **150c** rigidly in place relative to each other to enable handling and attachment of the hub to barrel connector **210c**, such adaptations including, for example, clippable flanges, interacting complementary fins and slots (such as illustrated fins **340** extending from hub body **168c** through corresponding slits **350** in sheath **170c** and engaging with corresponding slots in cap **180c**) or grooves and ridges, biasing means, and the like. In certain aspects cap **180c** may be closed and have a distal internal void large enough to take a priming volume or dose adjust volume of formulation and the void may also have an absorbent pad to absorb that volume.

[150] In certain aspects a valve, for example a duck valve, as well as the filter **300** may be provided between proximal body **168c1** and distal body **168c2** of the needle hub. Such a valve may be advantageous in inhibiting undesirable leakage of formulation from cartridge **240**, such as when residual pressures on the fluid or other forces exist that may move fluid out of the needle at undesirable moments in use of the device. .

[151] In certain aspects needle **64** may be made as short as possible (while still allowing for correct injection depth) to reduce formulation flow impedance.

[152] In use, an injection device according to this fourth embodiment, and with reference to figures 37 to 60, the device may be provided as a single-use, pre-packaged sterile device ready for injection, or it may be provided without formulation chamber, either embodiment optionally without needle hub **150c** (provided separately in a sterilised packaged form). If a formulation chamber **40** is provided separately, ideally pre-filled, actuation mechanism **20c** with sleeve **70c** is separated from elongated housing **10c** and formulation chamber **40** is inserted into elongated housing **10c** with crimped ring **248** and seal **246** resting against the radially intruding flanged surface provided by the proximal end of needle hub connector **210c**. Sleeve leaves **74c** are then re-positioned into elongated housing **10c** and actuation mechanism **20c** and elongated housing **10c** are brought together and fixed in position, at the same time engaging the distal end of plunger **80c** with stopper **50**. If the formulation chamber is vacuum or voidless filled, this assembly will result in positive pressure within formulation chamber **40**. As a result, proximal cap **290c** will sit elevated compared to actuation housing **110c**, and in a preferred embodiment this results in a gap 'A' between the distal surface of proximal cap **290c** and the corresponding resting surface of actuation housing **110c** (figures 52 and 37), as well as a gap 'B' between retention arm surface **125c** and

plunger ridge **82/86c**, gap 'A' being smaller than gap 'B'. Needle hub **150c** is then connected to needle hub connector **210c**, with plug **48** being removed first, and the proximal end of needle **62** pierces seal **246** and the positive pressure within formulation chamber **40** will result in plunger **80c** and connected proximal cap **290c** moving distally, with proximal cap **290c** coming to rest against the corresponding surface of actuation housing **110c** (i.e., gap 'A' is reduced to a zero gap - gap 'A' in figure 53) and expulsion of formulation from barrel **42** into needles **62** and **64**, resulting in self-priming of the system. At the same time, gap 'B' between retention arm surface **125c** and plunger ridge **82/86c** is also reduced to a small gap 'B''. Having reference to Figure 54, proximal cap **290c** is then turned slightly, reducing gap 'B' to 0, thereby calibrating the device. With reference to Figure 55, further rotation of proximal cap **290c** will move it proximally away from its complementary resting surface on actuation housing **110c**, creating gap 'A''' to set the dose travel distance, where it is ready to be triggered and deliver the set dose. Markings may be provided on the external surface of actuation housing **110c** which correlate with the proximal extension of proximal cap **290c** relative to actuation housing **110c**, and therefore the size of gap 'A''' and the dose equivalent to that gap and, optionally, proximal cap **290c** may have one or more windows in its outer surface for viewing such markings and setting the dose, as also described earlier for the third embodiment. The marking for any given dose may extend around the full circumference of the external surface of actuation housing **110c**, with regular dose markings associated therewith, to assist in dose setting while rotating proximal cap **290c** relative to actuation housing **110c**.

[153] This mechanism, which is applicable to not only the fourth embodiment, but also the third embodiment (i.e., embodiments of the present invention employing an actuation housing with a proximal cap, wherein the interaction between the proximal cap and the plunger define the dosing), makes it possible to remove tolerance variability in the specific device in hand, with accuracy of the distance to travel for dose release only being affected by minimal amounts of dimension tolerance variability at dose set point, providing a significant advantage in dose accuracy capability of the device. In addition, a spring may be included between proximal cap **290c** and plunger **80c** to take up any slack between proximal cap **290c** and plunger **80c**, to negate any play and corresponding effects on dose variability.

[154] Once the injector is primed and the dose set, restrainer **130c** will be in the distal, restraining position, with retention arm **120c** held against plunger **80c**, with inwardly directed ledge **125c** engaging with opposed ridge/ledge **82/86c** of plunger **80c**, thereby holding plunger in 'primed' position against bias provided by first spring **90**.

[155] Eye-contacting surface **177c** is then placed against the surface to which injection is to be made and pressure applied in a distal direction. This pressure results in sheath **170c** sliding proximally into elongated housing **10c** and against the distal ends of sleeve leaves **74c** and corresponding proximal sliding of sleeve **70c** up into actuation housing **110c** and against bias provided by second spring **190** being stressed between actuation housing ribs **330** and spring-engaging ridge **78c** on the outer circumferential edge of sleeve body **72c**. As sleeve **70c** moves proximally into the actuation housing restrainer **130c** also move proximally. Once restrainer **130c** has moved the required distance proximally (as a result of needle **64** reaching the desired injection depth) retention tabs **128c** are no longer held against plunger **80c** and, as a result, the bias provided by spring **360** deflects the 'arm' of retention arm **120c** away from plunger **80c** (with the abaxial deflection of the distal ends of retention arm **120c** being limited by the inner wall of sleeve body **72**), breaking the engagement of ledge **125c** and ridge/ledge **82/86c** and releasing plunger **80c** which, under pressure from driving spring **90**, is driven distally, resulting in formulation being expelled from the distal end of needle **64** and proximal cap **290c** again coming to rest against the corresponding surface of actuation housing **110c** (i.e., gap 'A' is reduced to a zero gap - gap 'A' in figure 56).

[156] Once injection has been performed, distally applied pressure is eased or removed and, as a result, sleeve spring **190**, applying pressure on ridge **78c** of sleeve **70c**, which is no longer opposed, urges sleeve **70c** distally, which in turn results in sheath **170c** being urged distally to once again cover needle **64**. Also, as a result of sleeve **70c** being urged distally, its inner wall no longer limits the further abaxial travel of retention arm **120c**, which then deflects further abaxially towards the wall of actuation housing **110c** (and radially outward of pivot point **390**), with distal edges of retention tabs **129c** then engaging with sleeve body **72c**, in a preferred embodiment with corresponding recesses/notches **370** formed in the outer rim of the distal end of sleeve body **72c**, thereby obstructing potential proximal travel of sleeve **70c** and therefore of sheath **170c**, thereby locking sheath **170c** into a needle covering position, making the device safe (figures 43 and 46). Instead of recesses/notches **370**, the proximal surface of sleeve body **72c** may comprise alternative means for engaging the distal edges of retention tabs **129c**. For example, the proximal surface of sleeve body **72c** which makes contact with the distal edges of retention tabs **129c** may comprise flexible fingers which more strongly engage the distal edges of retention tabs **129c** than a smooth or notched surface. Other means for ensuring strong engagement between sleeve body **72c** and the distal edges of retention tabs **129c**, to ensure a stronger locking of the sheath into a needle-covering position, will be readily apparent to those skilled in this art.

[157] In a fifth embodiment illustrated in figures 61 to 92, actuation mechanism **20d** may comprise an actuation housing **110d**, which comprises a proximal portion **260d** and a distal portion **270d**, wherein proximal portion **260d** has a narrower diameter and inner bore than distal portion **270d**. Distal portion **270d** of actuation housing **110d** is adapted to house driving spring **90**, the proximal half of plunger **80d**, a substantial portion of a retention toggle **120d** and restrainer **130d**. At its proximal end plunger **80d** has a threaded extension **280d** and extends proximally beyond actuation housing **110d** through channel **263d** and engages with thread **293d** in proximal cap **290d**, with at least one driving spring **90** positioned between the proximal end of actuation housing **110d** and plunger **80d**. Plunger **80d** may comprise any suitable means for holding driving spring **90** between plunger **80d** and distal surface **111d** of the spring retention flange of actuation housing **110d** (Figures 81 and 82), such as ridge **82d** shown in Figures 72 and 73 which in that particular aspect is formed at about the proximal third of plunger **80d**. In the embodiment illustrated, and with particular reference to Figures 63 to 69 and 80-82, actuation housing **110d** also comprises a retention ledge with proximal surface **112d** adapted to engage retention surface **122d** of toggle **120d** and a distal surface **113d** adapted to engage with lock out surface **128d** of toggle **120d**. Actuation housing **110d** may also comprise a lateral space extension **118d** to provide a space for the proximal end of toggle **120d** to move into once released (if the proximal end of toggle **120d** is needed to be so long – see Figures 67 to 69). In certain aspects, an aperture may be provided in the proximal side of extension **118d** and/or the actuation housing **110d** such that a user may view the proximal end of toggle **120d** through that aperture and ascertain that the injection device has been actuated. In certain aspects, indicators configured to indicate one or more of the actuation of the injection device, completion of the injection, confirmation of dose setting, and/or “lock out” of the device may be provided, including haptic indicators, auditory indicators, other visual indicators, one or more electronic signals optionally configured to interface with one or more other devices or applications, or other such indicators known to one having ordinary skill in the art.

[158] In certain aspects, proximal cap **290d** fits over actuation housing **110d** but is not fastened thereto, threading instead onto thread **280d** of plunger **80d** (which projects beyond actuation housing **110d**) via complementary thread **293d**, allowing for adjustment of proximal cap **290d** relative to plunger **80d** (and stopper **50**, not shown), and therefore for adjustment of dosage to be delivered, optionally monitored via markings **116d** on housing **110d** viewed through window **297d**. Dose setting may be facilitated by way of, for example, dose snap settings provided by, for example, dose setting snaps **114d** interacting with a dose setting snap recess **295d**, or perhaps by way of axially extending furrows spaced radially on the inside of proximal cap **290d**, with, for example, one snap per dose setting. Proximal cap **290d** may also optionally comprise a window **298d** through

which a user may see an indicator strip **117d** (optionally coloured) when the injection device is primed or when the dose has been delivered.

[159] In the embodiment illustrated in Figures 61 to 97, and especially figures 85 to 92, elongated housing **10d** comprises a hollow cylinder comprising an external thread **210d** at its distal end for engaging needle hub **50d**. In a further aspect centering ribs **220d** which extend proximally from the distal end of housing **10d** for at least a portion of the length of housing **10d** are provided which are adapted for holding and centering a formulation chamber, pre-filled syringe or cartridge **240** within the elongated housing. One or more of ribs **220d**, preferably two or three of said ribs support a cartridge seat **230d** provided in the form of a centrally 'floating' perforated disc as illustrated in figures 86 and 87. Elongated housing **10d** houses sleeve **70d**, at least one sleeve spring **190** and, when fitted, formulation chamber **240**, all three held in position in the elongated housing by cartridge centering/spring retaining plug **440**.

[160] In the embodiment illustrated in Figures 90 and 91, cartridge centering/ spring retaining plug **440** may comprise slits **442** through which leaves **76d** of sleeve **70d** may extend proximally, as described below, as well as spring retention/compression ring **444**, formulation chamber centering ribs and arms **446**, and in preferred embodiments centering/positioning features **447** and snap features **448** for securing plug **440** in position in elongated housing **10d**, thereby securing spring **190** and formulation cartridge **240** in position. In certain aspects plug **440** may be a separate object as illustrated in figures 90 and 91, or may be, for example, integrally formed as part of either actuation housing **110d** or even elongated housing **10d**.

[161] Elongated housing **10d** and actuation housing **110d** may engage with one another by any suitable means, such as those known in the art, which will ensure that in use they remain in a fixed positional relationship relative to one another. For example, the mutually compatible surfaces may be welded, pinned, crimped, snapped, screwed or glued together.

[162] In the specific embodiment illustrated in figures 61 to 92, and particularly Figures 88 and 89, sleeve **70d** comprises a hollow cylindrical central body **72d** with two opposed sleeve leaves **74d** extending distally from body **72d** and between ribs **220d** (and between housing **10d** and chamber **240**, if in position), said sleeve leaves comprising distal surfaces **73d** adapted to interact with complementary proximal surfaces of needle sheath **170d**. Optionally the gaps between sleeve leaves **74d** may coincide with a window in elongated housing **10d** such that the contents of formulation chamber **240** (if installed) can be viewed, such as window **18c** as described in the third embodiment. Alternatively, sleeve leaves **74d** or even all of sleeve **70d** may be transparent. In an

alternate embodiment, the elongated housing may be comprised of a transparent or translucent material to enable visibility of the formulation chamber and/or the internal mechanism contained within the elongated housing. In an embodiment sleeve **70d** also comprises leaves **76d** extending proximally from body **72d** between elongated housing **10d** and chamber **240** (if in position) and through corresponding slots **442** in plug **440** (see Figs 91 and 92) and comprising proximal surfaces **78d** adapted for interacting with complementary surfaces on restrainer **130d** and for pushing restrainer **130d** proximally when pressure is applied proximally by sheath **170d** to the distal surfaces **73d** of sleeve **70d**.

[163] Having reference to figures 63 to 69 and 77 to 79, when an injection device according to the present invention is put together, with formulation cartridge **240** in place and plunger **80d** engaged with stopper **50** (not shown), with dose set and the device primed for injection, driving spring **90** is held under stress with plunger **80d** held in position by retention toggle **120d**, with retention toggle **120d** being held in plunger-engaging position by restrainer **130d** which is at least proximally slidable, restrainer **130d** being in restraining position when distal (figure 77) and in releasing position when proximal (figures 78 and 79).

[164] Having reference to figures 61-92, and particularly figures 72-76, retention toggle **120d** and restrainer **130d** as used in the fifth embodiment are illustrated. In particular, retention toggle **120d** comprises a toggle with a pivot/fulcrum point **121d** adapted to engage a pin or axle **140c** (shoulder joint) provided about one third of its length from its distal end. Alternatively, pin(s) or axle(s) **140d** may be formed separately or even form part of toggle **120d**. Pin/axle **140d** connects toggle **120d** to plunger **80d** via corresponding joints or fulcrum points **390d**. Toggle **120d** also comprises an outwardly directed ledge **122d** positioned slightly proximally of pivot/fulcrum point **121d** and adapted to engage an opposed ridge or ledge **112d** formed on actuation housing **110d**. At its proximal end, toggle **120d** comprises an axially internal surface **124d** adapted to engage a complementary axially external surface **132d** on restrainer **130d** to hold toggle **120d** in an actuation housing-engaging position while restrainer **130d** is in its restraining position. Triggering pressure (i.e., the amount of proximally directed force that needs to be applied by sleeve **70d** against restrainer **130d**, and therefore distal force that needs to be applied against a surface to be injected) using such retention arm or toggle is inversely proportional to a/b where "a" is the distance between pivot point **121d** and the proximal surface **124d** and "b" is the adaxial extension distance of the edge of ledge **122d** compared to pivot point **121d**, so for a given bias strength provided by spring **90**, the longer "a" is, or the smaller "b" is, the smaller the force required to trigger the device, allowing for less discomfort to a subject being injected. The distances "a" and "b" can be selected

for particular injection devices for particular applications. For example, where the injection device is for intraocular injection, a low triggering pressure may be desired, so a value for a/b such that “b” is equal to or substantially smaller than “a”, such as a value for a/b of greater than 1, such as between 1 and 1000, may be desired. Toggle **120d** may also comprise a lockout ledge **128d** adapted to engage with distal surface **113d** of the retention ledge of housing **110d** and may also comprise a surface **126d** which engages with surface **79d** of sleeve **70** to provide a further lockout feature, whereby proximal movement of sleeve **70d**, and surface **79d** pushing against surface **126d** of retention toggle **120d**, pushing it against the inner wall of the actuation housing, jamming it.

[165] Having reference to the restrainer **130d** as illustrated especially in Figure 74, this is provided as one or more sleeve-engaging surfaces **134d** connected to a toggle-retaining surface **132d**. In use, restrainer **130d** moves proximally when sleeve **70d** is slid proximally relative to elongated housing **10d** by applying distal pressure on the injection device against a surface to be injected, thereby releasing toggle **120d** so as to allow surface **122d** to deflect adaxially (under bias from spring **90**) from ridge or ledge **112d** of actuation housing **110d**, allowing driving spring **90** to drive plunger **80d** and stopper **50** (not shown) distally. As illustrated in Figures 72 to 74, restrainer **130d** may comprise means for holding the restrainer in slidable connection with plunger **80d**. Such means may comprise, for example as illustrated, arms **136d** adapted to clip over ridges **85d** on plunger **80d**, thereby holding restrainer **130d** against plunger **80d** in a proximally-distally slidable relationship. In certain aspects restrainer **130d** may also comprise a protrusion **138d** adapted to pass through aperture **119d** in housing **110d** and engage with transportation locking bar **299d** of proximal cap **290d** (to prevent unintentional activation/movement) and slidably positioned in furrow **138d** in plunger **80d** (Figures 71, 72, 81 and 84). In other aspects, restrainer **130** may be formed as a ring fully encircling the plunger, removing the need for clip-on features. In yet other aspects the restrainer may have protrusions like **138d** but adapted to slide in corresponding furrows in the actuation housing: many other options for arranging locking protrusions will be apparent to those working in this field given the description above, and illustrations of the intended objective.

[166] With reference to figures 93-95, needle hub **150d**, which may be used with any of the second, third, fourth or fifth embodiments, may comprise a body **168d** having a proximal body **168d1** having a needle **62** extending proximally from it and a distal body **168d2** having a needle **64** extending distally from it, needle **62** being for piercing of the formulation cartridge seal **246** (if present – if a pre-filled syringe is used instead of a formulation cartridge, there will be no septum to pierce), and needle **64** being for insertion into a subject for injection. Distal body **168d2** is axially centered via ribs **164d** within a connector **166d** adapted to engage and connect with barrel

connector **210d**. Bodies **168d1** and **168d2** are adapted to connect together (and may, for example, be snapped together, glued or ultrasonically welded), with a filter **300** enclosed between the two bodies for filtration of any particles that may be generated in piercing the prefilled cartridge or prefilled syringe, or any microparticulate matter present in the formulation. Sheath **170d** comprises a distal subject-contacting surface **172d** and proximal leaves **174d**. Proximal sheath leaves **174d** pass slidably through slits **167d** between needle hub body **168d2** and connector **166d**, and the proximal end surfaces of leaves **174d** are adapted to engage the distal surfaces **73d** of leaves **74d** of sleeve **70d** when hub **150d** is fully connected with barrel connector **210d**. Proximal sheath leaves **174d** may also be flexible and comprise snap-tabs for securing the sheath in an interleaved relationship with barrel connector **166d** (see Figure 95). When not in use, hub **150d** (whether attached to connector **210d** or not) may comprise a removably attachable cap **180d**. The cap may be adapted to support, protect, or both support and protect the sheath (and the patient-contacting surface) in its extended position and from contact with external surfaces. In a further embodiment, the removably attachable cap may further have a feature adapted to surround the needle when the removably attachable cap is connected to the needle hub. In certain embodiments, such a feature may be further adapted to receive volume of the formulation expelled during priming of the injector for use. The distal end of sheath **170d** may comprise a guide for securing and protecting needle **64** within the needle hub and during injection. Subject-contacting surface **172d** may comprise a pad made of softer and/or spongier and/or adherent material than sheath **170d**, such as silicone or rubber. Alternatively, the distal end of sheath **170d** may be provided with a rough or even spiky surface to assist in keeping the injection device in position during the injection procedure. In further embodiments the distal surface of sheath **170d** may be provided with features such as protrusions, ridges and/or other textural elements. In yet further embodiments, the contacting surface of the distal surface of sheath may include a combination of the aforementioned features or materials. Such materials and features may assist in holding the distal surface in position (for example in the correct injection position on the eye surface for intraocular injection) during the injection procedure, and may further assist the clinician in controlling or retaining the position of the eye in a desirable position during the injection. Although not shown, needle hub **150d** may comprise a biasing means, such as a spring, within sheath **170d**, which urges sheath **170d** distally with respect to body **168d** and therefore needle **64**, to keep needle **64** sheathed when not in use.

[167] As described earlier for another needle hub embodiment, in certain aspects a one way valve, for example a duck valve may be provided between proximal body **168d1** and distal body **168d2** of the needle hub. Such a valve may be advantageous in inhibiting undesirable leakage of formulation from cartridge **240** when positive pressure exists, such as when residual pressures on the fluid or

other forces exist that may move fluid out of the needle at undesirable moments in use of the device.

[168] In certain aspects needle **64** may be made as short as possible (while still allowing for correct injection depth) to reduce formulation flow impedance. In other aspects any space between needles **62** and **64** inside the needle hub may be as wide and/or be of the same diameter as needle **62**, or may have other geometric adaptations configured to reduce formulation flow impedance. In other aspects needle **62** may have a split channel to allow for the escape of any air trapped in the needle hub during priming and/or injection.

[169] Other optional features of needle hubs according to the invention have already been described above in relation to at least the fourth embodiment and apply to this embodiment equally.

[170] In use, an injection device according to this fifth embodiment, and with reference to figures 61 to 95, the device may be provided as a single-use, pre-packaged sterile device ready for injection, or with a prefilled syringe, or with a cartridge intended to be utilized with multiple patients with separable needle hubs, or it may be provided without formulation chamber, either embodiment optionally without needle hub **150d** (provided separately in a sterilised packaged form). If a formulation cartridge **240** is provided separately, ideally pre-filled, actuation mechanism **20d** and optionally plug **440** (cartridge-centering arms **446** may be sufficiently flexible to allow cartridge **240** to pass through without the need to remove plug **440**) are separated from elongated housing **10d** and formulation cartridge **240** is inserted into elongated housing **10d** with crimped ring **248** and seal **246** (as illustrated in Figures 21 and 22) resting against seat **230d**. Plug **440** is then reinserted into the proximal end of elongated housing **10d** (compressing spring **190**), if it was removed, and actuation mechanism **20d** and elongated housing **10d** are then brought together and fixed in position, at the same time engaging the distal end of plunger **80d** with stopper **50**. If the formulation cartridge is vacuum or voidless filled, this assembly will result in positive pressure within formulation cartridge **240**. As a result, proximal cap **290d** will sit elevated compared to actuation housing **110d**, and in a preferred embodiment this results in a gap 'A' between the distal surface of proximal cap **290d** and the corresponding resting surface of actuation housing **110d** (figure 63), as well as a gap 'B' between toggle surface **122d** and proximal surface **112d** of the retention ledge of actuation housing **110d**, gap 'A' being smaller than gap 'B'. Needle hub **150d** is then connected to needle hub connector **210d**, and the proximal end of needle **62** pierces seal **246** and the positive pressure within formulation cartridge **240** will result in plunger **80d** and connected proximal cap **290d** moving distally, with proximal cap **290d** coming to rest against the corresponding surface of

actuation housing **110d** (i.e., gap 'A' is reduced to a zero gap - gap 'A' in figures 64 and 65) and expulsion of formulation from cartridge **240** into needles **62** and **64**, resulting in self-priming of the system. At the same time, gap 'B' between toggle surface **122d** and proximal surface **112d** of the retention ledge of actuation housing **110d** is also reduced to a small gap 'B' (Figure 64). Having reference to Figure 65, proximal cap **290d** is then turned slightly, reducing gap 'B' to 0, thereby calibrating the device. With reference to Figure 66, further rotation of proximal cap **290d** will move it proximally away from its complementary resting surface on actuation housing **110d**, creating gap 'A''' to set the dose travel distance, where it is ready to be triggered and deliver the set dose. Markings may be provided on the external surface of actuation housing **110d** which correlate with the proximal extension of proximal cap **290d** relative to actuation housing **110d**, and therefore the size of gap 'A''' and the dose equivalent to that gap and, optionally, proximal cap **290d** may have one or more windows in its outer surface for viewing such markings and setting the dose, as also described earlier for the third embodiment. The markings for doses may extend around the circumference of the external surface of actuation housing **110d**, to assist in dose setting while rotating proximal cap **290d** relative to actuation housing **110d**.

[171] This mechanism, which is applicable to not only this fifth embodiment but also the fourth and third embodiments (i.e., embodiments of the present invention employing an actuation housing with a proximal cap, wherein the interaction between the proximal cap and the plunger define the dosing), makes it possible to remove tolerance variability in the specific device in hand, with accuracy of the distance to travel for dose release only being affected by minimal amounts of dimension tolerance variability at dose set point, providing a significant advantage in dose accuracy capability of the device. In addition, a spring may be included between proximal cap **290d** and plunger **80d** to take up any slack between proximal cap **290d** and plunger **80d**, to negate any play and corresponding effects on dose variability.

[172] In an alternative embodiment of a priming mechanism needle hub assembly **150d** may also comprise a priming spring at the proximal end of proximal body **168d1** which is narrower in diameter than the aperture in seat **230d** such that it pushes against cartridge **240** proximally when needle hub **150d** is threaded onto barrel connector **210d**. In such an embodiment plug **440** may also comprise internally protruding cartridge stops on formulation chamber centering ribs and arms **446** so that when needle hub **150d** is threaded onto barrel connector **210d** the priming spring pushes cartridge **240** towards the cartridge stops which also moves stopper **50** towards and eventually engaging with the distal surface of plunger **80d** before the proximal surface of cartridge **240** reaches the cartridge stops providing a gap 'x'. Further threading of needle hub **150d** onto barrel connector

210d results in plunger **80d** pushing on stopper **50** creating positive 'priming' pressure in cartridge **240** between the priming spring and plunger **80d** (proportional to the spring force and deflection of the priming spring in the hub). Further threading of needle hub **150d** onto barrel connector **210d** results in further compression of the priming spring and needle **62** piercing septum **44** with formulation then passing through the needle hub to allow pressure equalisation, which also allows further proximal travel of cartridge **240** until its proximal surfaces reach the cartridge stops on plug **440** (i.e., reducing gap 'x' to 0), with a concomitant amount of formulation passing through the needle assembly, thereby priming the needle hub **150d**. In such a system the positive pressure generated in cartridge **240** between the priming spring and plunger **80d** is smaller than would be applied by spring **90** in the embodiment described earlier, reducing delayed pressure-related leakage after piercing of septum **246** (which may occur especially with viscous formulations) and to also prevent loading of the stopper and, thereby preventing pressurization of the fluid and subsequent, sustained loading of the septum during storage. In other aspects needle **62** may have a split channel to allow for the escape of any air trapped in the needle hub during priming and/or injection.

[173] Once the injector is primed and the dose set, restrainer **130d** will be in the distal, restraining position, with toggle **120d** held so as to have toggle surface **122d** engaged with proximal surface **112d** of the retention ledge of actuation housing **110d**, thereby holding plunger **80d** in 'primed' position against bias provided by first spring **90**.

[174] Patient-contacting surface of sheath **172d** is then placed against the surface to which injection is to be made and pressure applied in a distal direction. This pressure results in sheath leaves **174d** sliding proximally into elongated housing **10d** and against the distal ends **73d** of sleeve leaves **74d** and corresponding proximal sliding of sleeve **70d** and sleeve leaves **76d** up into actuation housing **110d** and against bias provided by sleeve spring **190** being stressed between spring retention ring **440** and spring-engaging ridge **77d** on the inner circumferential edge of sleeve body **72d**. As sleeve **70d** moves proximally into the actuation housing, proximal surfaces **78d** of sleeve leaves **76d** also move proximally into the actuation housing **20d**, eventually engaging surfaces **134d** of restrainer **130d** sliding it proximally. Once restrainer **130d** has moved the required distance proximally (as a result of needle **64** reaching the desired injection depth) retention surface **132d** no longer engages surface **124d** of toggle **120d**, allowing toggle **120d** to rotate about axis **121d** (as a result of bias applied by spring **90**) and disengaging surfaces **122d** and **112d**, thereby releasing plunger **80d** to be driven distally under the bias provided by spring **90**, resulting in formulation being expelled from the distal end of needle **64** and proximal cap **290d** again coming to rest against the

corresponding surface of actuation housing **110d** (i.e., gap 'A' is reduced to a zero gap - gap 'A' in figure 65).

[175] Once injection has been performed, distally applied pressure is eased or removed and, as a result, sleeve spring **190**, applying pressure on ridge **77d** of sleeve **70d**, which is no longer opposed, urges sleeve **70d** distally, which in turn results in sheath **170d** being urged distally to once again cover needle **64**. Also, as a result of sleeve **70d** being urged distally, its inner wall no longer limits the further abaxial travel of surface **126d** of toggle **120d**, which under the bias of spring **360d** then deflects further abaxially towards the wall of elongated housing **10d** (and radially outward of pivot point **121d**), with surface **126d** then engaging with surface **79d** of sleeve body **72d** if sleeve **70d** and sheath **170d** are urged proximally for any reason, thereby locking sheath **170d** into a needle covering position, thereby reducing the risk of needlestick injury by disallowing the distal needle from being re-exposed to the user (Figure 69). Other means for ensuring strong engagement between sleeve body **72d** and the distal edges **126d** of toggle **120d**, to ensure a stronger locking of the sheath into a needle-covering position, some of which have already been discussed above in relation to other embodiments will be readily apparent to those skilled in this art.

[176] Having reference to drawings 96 and 97 an alternative embodiment relating to dosage mechanisms is illustrated which allows for greater sensitivity and accuracy in setting small doses (for example, doses of 100µL or less). In this embodiment proximal cap **290d** (as described for the fifth embodiment) is replaced by internal dose setting knob **290e** with a thread **294e** which threads onto thread **280e** of plunger **80e** (which may be identical to plunger **280d** described earlier). The outside surface of internal knob **290e** may be of a suitable shape such that external knob **500e** slides over internal knob **290e** but internal knob **290e** and external knob **500e** cannot significantly rotate axially relative to one another. Such shape on the outside surface of internal knob **290e** may comprise square or oblong cross-section, and/or may involve splines or the like which engage with complementary inner surfaces in external knob **500**. External knob **500e** comprises an external surface with a thread complementary to a thread **510e** on the inside surface of extended section **115e** of actuation housing **110e**. Thread **510e** has a pitch which is significantly larger than the pitch of thread **280e/294e** so that when knob **500e** is turned anti-clockwise by one full turn, with concomitant turning of internal knob **290e** by one full turn, knob **500e** travels proximally (compared to the rest of actuation housing **110e**) by a significantly greater distance than does internal knob **290e**, the benefit being that a large proximal movement of knob **500e** results in small proximal travel of internal knob **290e** with concomitant small change in amount of dose to be delivered by the device, allowing for greater visual ease in setting small doses for injection by devices according to

the present invention. For yet greater convenience, internal knob **290e** may comprise flexible extended arms **296e** with pips that engage with grooves **520e** arranged radially and distally on the inside surface of extended section **115e**, as illustrated in Figure 97 to allow for stepped dosing measurements. As illustrated in Figure 96A, extended section **115e** may also comprise a window **530e** for viewing dose settings located on the external surface of external knob **500e**, and optionally a window **540e** which allows for viewing of whether internal knob **290e** has returned to its resting position after actuation, thereby confirming that the device has been actuated and the dose delivered. Parameters such as the number of turns of the dose setting knob to maximum dose, the pitch of the internal dose setting knob thread, diameter of housing **115e**, size and number of detents **520e** within the inner circumference of housing **115e** may all be adjusted to tailor a given device for specific dose volumes and increments and accuracies.

[177] In an alternative to the embodiment illustrated in Figures 96 and 97, and as illustrated in Figure 98, extended section **115e** of actuation housing **110e** is replaced by a separate dose delivery housing **115f** into which external knob **500f** threads via complementary threads as described above for components **115e** and **500e**, with knob **500f** being adjusted until a '0' reading is observable in window **530f** before fitting external knob **500f** over internal knob **290f**, which may be the same as internal knob **290e** as described above, or which may comprise a multitude of radially arranged proximally-distally extending splines **295f** adapted to engage one or more complementary surfaces, such as ridges on the inside of external knob **500f**. Dose delivery housing **115f** is then connected to actuation housing **110f** in a fixed manner/position (i.e.. such that dose delivery housing **115f** does not rotate or move proximally or distally significantly). The benefit of this embodiment is that, once delivery housing **115f** is fixed in position on actuation housing **110f**, dose external knob **500f** is set to a '0' setting. The '0' setting is achieved by having the retention toggle surface **122d** engage with actuation housing surface **112f** (i.e. there is no gap between the two, they are in contact), then internal knob **290f** is rotated until it contacts actuation housing **110f**, or nearest detent (which could result in very small gap between **295f** and **110f**) or, alternatively, a very small gap may be present between surfaces **122f** and **112f** (because plunger **80f** is raised and spring **90** compressed, raising retention toggle **120e** off the ledge) which can be controlled as desired by the thread pitch on **290f**. Assembly **115f/500f** is then fitted over internal knob **290f** as the spline pattern on **500f** matches the spline pattern **295f**, and the system is correctly set at 0.

[178] With reference to Figures 99 and 100, a self-setting retention arm mechanism is described, which is applicable to the embodiments having a retention toggle. In such an aspect, a slightly modified retention toggle **120f** has a bevelled or rounded surface **125f** and has a slightly elongated

surface **128f** compared to surface **128d** of the retention toggle illustrated in Figures 75 and 76. Also, as well as a retaining surface **132f** (corresponding with retaining surface **132d** in Figure 74), restrainer **130f** comprises a bevelled/rounded surface **133f** adapted to engage slidably with surface **125f** of retention toggle **120f**. Once the actuation mechanism is assembled, proximal pressure applied to plunger **80d/e/f** pushes surface **128f** proximally until it engages surface **113d/e/f** on the inside of actuation housing **110d/e/f**. Continued proximal pressure applied to plunger **80d/e/f** causes retention toggle to pivot about pivot axis **121f**, against bias applied by spring **360f** and aligning retention toggle **120f** with plunger **80d/e/f** and bringing bevelled/rounded surface **125f** of retention toggle **120f** in contact with surface **133f** of restrainer **130f**, such that continued proximal pressure on plunger **80d/e/f** results in abaxial pressure by surface **125f** being applied to surface **133f**, such that restrainer **130f** is pushed proximally, against bias applied by spring **90** (not shown), until surface **125f** and surface **124f** have moved abaxially relative to retaining surface **132f** at which point restrainer **130f** is again free to move distally under its own weight (or optionally under bias applied to the proximal surface of restrainer **130f**) until restrainer **130f** comes to rest on a complementary surface on plunger **80d/e/f**. Removal of proximal pressure on plunger **80d/e/f** then allows the bias of spring **360f** and spring **90** to apply pivotal pressure on retention toggle **120f** such that surface **124f** is pushed against retention surface **132f**, stopping further pivoting of retention toggle **120f** and also allows plunger **80d/e/f**, restrainer **130f** and retention toggle **120f** to move distally under bias from spring **90** until surface **122f** of retention toggle **120f** comes into contact with surface **112f** of actuation housing **110f**, stopping further distal movement of the assembly such that the actuation mechanism is now in an activated configuration, ready for triggering.

[179] Having reference to Figure 108, with a particular focus on Figure 108 G', in the context of the dosage mechanism illustrated in Figure 98 and described above, the self-setting retention arm mechanism illustrated in Figures 99 and 100 and described above lends itself to an injection device which can be re-set for multiple injections using the same actuation mechanism, with the same elongated housing (with or without replacement of formulation chamber(s)), or replacing the elongated housing (again, with or without replacement of formulation chamber(s)). In the specific embodiment illustrated in Figure 108, the formulation chamber **240f** is formed integrally with the elongated housing **10f**, being connected to inside of the wall of the elongated housing by axially inwardly extending ribs. However, the mechanism described here can operate with embodiments as described earlier involving separate formulation chambers, such as syringes and cartridges, which may be replaceable. Sleeve **70f** is slidably positioned between formulation chamber **240f** and the wall of the elongated housing **10f**, and sleeve **70f** is biased distally by sleeve spring **190** (held in place against sleeve **70f** by spring retention ring **440**) and is adapted to engage the distal end of restrainer

130f. Restrainer **130f** in turn engages with the proximal surface **124f** of toggle **120f** which is connected to plunger **80f** via pivot point **121f** as described above. In the specific embodiment illustrated in Figure 108, needle sheath **170f** is formed separately to sleeve **70f**, but is adapted to engage the distal end of sleeve **70f** and therefore when sheath **170f** is positioned against a target portion of anatomy to be injected and the injection device urged distally, sheath **170f** pushes against sleeve **70f** which slides proximally as a result and in turn pushes restrainer **130f** proximally to release proximal surface **124f** or toggle **120f** which is then free to pivot from its unactuated position to its actuated position, thereby releasing plunger **80f** to be impelled distally by spring **90**, as described previously. Whilst the embodiment specifically illustrated in Figure **108** has a sheath **170f** formed separately to with sleeve **70f**, the mechanism described here may also operate with needle sheaths that are integrally formed with sleeves **70**. Furthermore, whilst the embodiment specifically illustrated in Figure **108** has an integrally formed needle (which is glued or overmoulded into position), the mechanism described here may also operate with formulation chambers which have their own needle assemblies, or with elongated housing with detachable/replaceable needle hubs as per any of the embodiments described previously. Importantly, the injection device illustrated in Figure **108** comprises a modification to the dose delivery mechanism illustrated in Figure 98 and described above, the modification being that dose delivery housing **115g**, as compared to dose delivery housing **115f** illustrated in Figure 98 and described above, has a circumferentially outwardly extending flange or flanges **670** which may be used to pull the dose delivery mechanism proximally to effect the toggle re-set as illustrated in Figure 98 and described above. Such a flange is not necessary, and dose delivery housing **115f** or a different modification to that shown in Figure 108 may be equally effective (dose delivery housing **115f** may for example simply be pulled proximally, and perhaps have a rough external surface to assist in this). Dose delivery housing **115g** may optionally comprise a distally extending extension **680** as illustrated, which fits slidably over the actuation housing, optionally clipping over the extension housing and being secured there (such that pulling of the dose delivery housing off the injection device is impeded) via ledge **690** extending inwardly from dose delivery housing **115g** and ledge **700** extending outwardly from actuation housing **110f**.

[180] Instead of circumferentially outwardly extending flange or flanges **670** to pull the dose delivery housing proximally, a twist ring could be positioned below a modification of **115g** or **115f** such that the dose delivery housing rests on the twist ring which engages the actuation housing via a complementary thread system such that, when the twist ring is rotated axially, it moves proximally, pushing the dose delivery housing proximally to effect the re-setting mechanism described above. When released, the twist ring may return to its starting position under pressure from the driving

spring 90, or may remain in any position between its fully twisted position or its starting position, if a non-zero dose is set on the dose delivery mechanism, but the twist ring will return to its starting position if and when the actuation mechanism is triggered. With such a configuration, the pitch of the actuation housing to twist ring thread can be customised to move axially at a desired distance per angle of rotation, but the pitch must not inhibit the twist ring from rotating back to its starting position. Alternatively, or in addition, a spring could be provided to drive the twist ring back to its start position after every reset action.

[181] Having reference now to the procedure illustrated in Figure 108, this relates to a multi-use injection device adapted for use and replacement of pre-assembled elongation housings, having pre-filled formulation chambers (which may or may not be integrally formed with the elongated housing. As shown in Figure 108A and 108B (and corresponding cross-section views 108A' and 108B'), a pre-assembled elongated housing **10f** (with components **70f**, **190**, **440** and **240**) is fitted onto plunger **80f** and the elongated housing then brought together with actuation housing **20g** (already pre-zeroed as described above in relation to the mechanism illustrated in Figure 98) and connected thereto by any suitable means, such as by a twist lock mechanism as illustrated in Figure 108B, which results in plunger **80f** contacting the formulation chamber stopper, pushing it distally and associated priming of distal needle **60** (see Figure 108B'; white arrow pointing downwards). A dose is then set by adjusting dose setting knob **500g** (Figures 108C' and 108C'), needle cap **180f** is then removed (Figures 108D and 108D'), sheath **170f** is positioned against a surface to be injected (not shown), distal pressure is applied to the injection device, resulting in sheath **170f**, sleeve **70f** and restrainer **130f** sliding proximally with toggle **120f** being released to pivot to its actuated position and plunger **80f** being driven distally by spring **90** to deliver formulation from formulation chamber **240** (Figures 108E and 108E'). Once injection has been performed, distal pressure on the injection device is removed, and sleeve spring **190** then biases sleeve **70f** and sheath **170f** distally such that sheath **170f** once again fully enshrouds needle **60** (Figures 108F and 108F'). At the same time toggle **120f** further pivots to its fully pivoted position such that surface **126f** is in contact with the inside wall of elongation housing **10f**, and surface **113g** (equivalent of surface **113f** as illustrated in Figure 100) of actuation housing **20g** and surface **128f** of toggle **120f** engage, to enforce lock out, whereby proximal sliding of sleeve **70f** and sheath **170f** (and exposure of needle **60**) is impeded. Before or after removal of the assembled, but now used elongated housing assembly, the actuation housing may then be re-activated as illustrated in Figure 108G, 108G' and 108G'', with reference also to Figures 99 and 100 and the associated description above in relation to the mechanism. As illustrated in Figures 108G and 108G', proximal pressure on optional flange(s) **670** assists in the proximal

motion of dose delivery housing **115g** to slide plunger **80f** proximally and pivot toggle **120f** back to its unactuated position and, as shown in Figures 108G'' and 98, relaxation of proximal pressure on dose delivery housing **115g** results in sleeve **70f** sliding distally and allowing restrainer **130f** to again engage surface **124f** of toggle **120f** to hold it in its unactuated position, resulting in the actuation housing being re-set. If the assembled elongated housing was not removed before re-setting of the actuation housing, it can now be removed to provide the actuation mechanism ready for attachment of a fresh, pre-assembled elongation housing having a fresh, pre-filled formulation chamber, ready for performing another injection, as per the procedure described above.

[182] Also having reference to Figures 108A to 108C (and corresponding cross-section illustrations 108A' to 108C'), a modified needle cap assembly is illustrated which assists in avoiding loss of formulation from the formulation chamber or engaged needle and support and protect the needle when not in use. While the needle illustrated in Figure 108 is integral with the elongation housing (being glued, overmoulded with, or otherwise fixed to the elongation housing), the cap configuration illustrated may be used with other needle assemblies, including replaceable needle hubs as also described earlier, optionally with adaptation(s) that ensure that the needle hub can be attached to the elongated housing (for example, to ensure that the cap does not slip or slide axially around the needle assembly body when the needle assembly is attached to the elongated housing by a twisting action). The cap **180f** illustrated in Figures 108A to 108C (and Figures 108A' to 108C') has a tip section **640** distal to the elongated housing and which is at least partially held within the proximal portion of cap body **180f** in a slidable relationship, such that tip section **640** can slide at least distally if not also proximally within the cap body **180f**. Tip section **640** also has a seal **650** made of a pierceable material, such as a spongy, resilient or rubbery material positioned inside in a manner such that the proximal end of sheath **170f** can slide between the inner wall of tip section **640** and seal **650**, and seal **650** engages with needle **60** in a sealed manner (for example, needle **60** pierces seal **650** at least partially) and, at the same time, may assist in supporting needle **60** while not in use. When needle **60** is in fluid communication with a formulation chamber under pressure (such as when the formulation chamber stopper is biased distally by plunger **80f** during priming), this pushes formulation through needle **60**, which then results in the formulation pushing seal **650** distally, which in turn results in tip section **640** being slid distally in relation to cap body **180f**, as well as priming of needle **60**. Seal **650** may optionally include a space **660** at the proximal end of the seal (which may remain within the distal end of sheath **170f** even after priming) which acts as a reservoir for accepting fluid expelled from needle **60**, such as during priming.

[183] Having reference to Figures 101 and 102, a cammed retention toggle **120g** is illustrated, which does not require a biasing spring **360d/e/f** for pivoting about axis point **121g** once triggered. Once the actuation mechanism is triggered by proximal movement of restrainer **130g**, and therefore uncoupling of surfaces **124g** and **132g**, plunger **80g** and connected retention toggle **120g** are driven distally by spring **90**, resulting in pressure between surface **123g** of retention toggle **120g** and surface **112g** of actuation housing **110g**, resulting in retention toggle **120g** pivoting about axis **121g** as a result of the rounded nature of surface **123g** until surface **123g** has pivoted adaxially to the extent that plunger **80g** is free to travel distally. As a result of the pivoting of retention toggle **120g** about axis **121g**, lock out extension **126g** pivots abaxially and comes into contact with and is pushed against the inner surface of sleeve surface **79g**. According to one embodiment, lock out extension may be flexible, or at least be flexibly attached to retention toggle **120g** and, as a consequence, it may be bent as a result of it being pushed against the inner surface of sleeve surface **79g** but, when triggering pressure is removed from sleeve **70g**, surface **79g** slides distally (as a result of bias by spring **190** on sleeve **70g**, not shown) and beyond lock out extension **126g**, which then deflects into the space vacated by surface **79g**. Further proximal pressure applied to sleeve **70** will then result in surface **79g** coming into contact with, and its further proximal travel being stopped by, lock out extension **126g**. Thus, if a needle hub with sheath is attached, proximal travel of the sheath is also inhibited by lock out extension **126g**, thereby keeping needle **64** sheathed after the mechanism has been actuated.

[184] In all embodiments of injection devices according to the present invention, driving spring **90**, which urges plunger/ plunger **80** distally (and therefore provides the force which expels formulation from formulation cartridge or chamber **40** or **240**) may be replaced by any other suitable biasing mechanism. For example, and as illustrated in Figures 103 and 104, a torsion spring may be used instead. In such an embodiment torsion spring **90h** has proximal pin **94h** which engages with a complementary slot **111h** in the proximal end of actuation housing **110h** and distal pin **92h** which engages with complementary slot **555** in torque nut **550**. Torque nut in turn engages with thread **82h** on plunger **80h**. When the actuation mechanism is assembled and ready for triggering, torsion spring **90h** is wound up and has stored energy. When the mechanism is triggered, as described previously, torsion spring **90h** unwinds, turning torque nut **550**, in turn driving plunger **80h** distally. The relationship between the torque diameter (defined by the position of slot **555** and the rotational axis of torque nut **550**) and the pitch of thread **82h** determines the mechanical advantage of the system.

[185] Figures 105 to 107 illustrate other possible mechanisms for pushing plunger 80 distally, optionally with mechanisms for securing the device and/or reducing the load on the plunger until intended to be actuated.

[186] For example, as shown in Figure 105, the spring or other resilient pulling means (for example a constant force spring 90b or extension spring 90c) may be offset from plunger 80i and exert bias on a lever arm 560 via point 564, the lever arm also may fit around plunger 80i and be connected to the actuation housing via axle point(s) 562. Lever arm 560 also has recessed space(s) 566 for engaging plunger pin 82i (which may extend on both sides of plunger 80i such that, when the spring or other resilient pulling means exerts its bias on point 564 of the lever arm 560, lever arm pivots distally about axle point(s) 562, and exerts distal pressure on plunger pin 82i, and therefore on plunger 80i. The leverage or mechanical advantage obtained using such a mechanism is provided by the ratio of distance between 564 and 562 and the distance between 566/82i to 562. Optionally removable tab 564 may hold lever arm in position while the device is idle (for example while being in storage or being transported), thereby inhibiting actuation of the device and exertion of pressure on plunger 80i (and formulation cartridge 240, if installed) until desired.

[187] As shown in Figure 106, a torsion spring 90d may be offset from plunger 80j and exert bias on a gear lever 580 having gear cogs 585 at its axle end which interact with corresponding teeth on plunger 80j. Torsion spring 90d has a body 92d, which fits around the gear lever axle 587, an arm 94d which engages the adaxial side of gear lever 580 and an opposite arm 94d which engages a complementary surface, slot or edge on the actuation housing opposite the point of connection of gear lever 580. Arm contact distance from axis of gear lever 580 versus diameter of gear teeth engaging with plunger 80j provides the mechanical advantage. When torsion spring 90d exerts its bias on gear lever 580, deflecting gear lever 580 abaxially as a result of rotation about its axle 587, gear lever cogs 585 engage corresponding teeth on plunger 80i, pushing plunger 80i distally. The abaxial deflection of gear lever 580 may also act as a visual indicator showing that the device has been actuated. Torsion spring 90d may be already wound, and gear lever 580 being under bias therefrom when the injection device is assembled or, optionally, the device may comprise a switch, such as lever 590, which may be operated to wind torsion spring 90d when ready to use the injection device.

[188] As shown in Figure 107, an alternative geared mechanism is illustrated where a compression spring 90e, offset from plunger 80k engages with a cogged rack 600 having cogs 605. Cogged rack 600 engages the abaxial side of gear 610 which also has an adaxial side that engages plunger 80k. The abaxial side of gear 610 engages the toothed rack cogs with corresponding cogs 612, and the

adaxial side of gear **610** has cogs which engage corresponding cogs **82k** on plunger **80k**. When compression spring **90e** exerts its bias on cogged rack **600**, it pushes it proximally, thereby also pushing the abaxial side of gear **610** proximally making gear **610** pivot about its axis **616**, in turn pushing its adaxial side and cogs **614** distally, thereby also pushing plunger **80k** distally. Compression spring may already be compressed when assembled (and, for example, stored) or, optionally, the injection device may comprise a compression button **620** for compressing spring **80k** when the injection device is ready for use.

[189] The alternative biasing mechanisms illustrated in Figures 103 to 107 have the advantage of providing greater mechanical advantage, and therefore applying greater injection force with smaller biasing devices, such as springs, which may be particularly advantageous when injecting high viscosity formulations.

[190] In certain other embodiments of injection devices according to the present invention, unintended early actuation of the device may be avoided through a locking mechanism that interacts with a restrainer as described herein in such a way as to stop it moving longitudinally along a distal-proximal axis. Such a mechanism may include, for example, a pin or stiff slip that passes through the actuation mechanism housing and into a corresponding berth or slit formed in the side or other part (such as an extension) of the restrainer. Alternatively, the outer perimeter of the restrainer, or more preferably a distal extension of the restrainer within the diameter of the restrainer, may comprise a partial ridge/flange with lateral abaxial groove that engages with a flange extending adaxially from the actuation housing and, in such an embodiment, clockwise or anticlockwise movement of the proximal cap, such as when setting the dose, will result in disengagement of that relationship, freeing restrainer to move. An exemplary locking mechanism is illustrated in figures 35-60, where sleeve **70c** has a proximally extending rod **320** that extends through slot **380** in the proximal end of actuation housing **110c**, and which is then impeded by corresponding blocking surface **410** formed in a channel **420** in the underside of proximal cap **290c** when in place. When proximal cap **290c** is turned to calibrate the system and set the dose, as described earlier, surface **410** no longer covers the proximal end of rod which is now free to move into channel **420**, thereby unlocking the device and allowing sleeve **70c** to move proximally. Other such releasable locking mechanisms can be readily conceived by those working in this field.

[191] In other aspects as illustrated in figures 57 to 60 (and which is relevant to not only the fourth embodiment, but also the third embodiment - i.e.. embodiments of the present invention employing an actuation housing with a proximal cap, wherein the interaction between the proximal cap and the plunger define the dosing), the relationship between proximal cap **290c** and actuation housing **110c**

may be stabilised so as to not allow free axial rotation of proximal cap **290c** relative to actuation housing **110c**, and therefore alteration of dose for example, during the injection procedure. One means of achieving this is a ratchet mechanism as illustrated in figures 57-60, wherein a biased pawl **400** is provided on the perimeter of actuation housing **110c** and proximal-distal indentations **430** are provided on the inner surface of proximal cap **290c** such that, when proximal cap **290c** is placed in position over actuation housing **110c** (with proximal cap **290c** and actuation housing **110c** being a close fit with one another), biased pawl **400** interacts with indentations **430** such that sufficient force is required to overcome that interaction to rotate proximal cap **290c** relative to actuation housing **110c**. Other mechanisms for stabilising the relationship between proximal cap **290c** and actuation housing **110c** will be readily apparent to those in this field and may include, for example, a friction fit or mechanism.

[192] In various embodiments/aspects of the injection devices according to the present invention plungers may be composed of two or more parts instead of being a single body. For example, one part of a plunger in a device according to the present invention may have a toggle and the dose setting mechanism attached thereto which a second part may be provided by the formulation chamber (for example attached to stopper). Thus, It will be understood to one having ordinary skill in the art that plunger could be construed to mean a plunger provided as one integral piece, or a mechanism having multiple components which combine to create a plunger as described in this invention.

[193] As mentioned above, a person skilled in the art given the benefit of the above teachings will be able to derive alternative embodiments, including devising alternative actuation mechanisms which operate in the same manner using no more than materials and designs that are either already well known to those working in the field of injection devices or which would involve no more than routine workshop variations of what has been described above.

[194] Devices according to the present invention may be used for injection of any formulation, including liquid, solid (e.g. film, implants, gels, or particle(s)), suspensions, or semi-solid or phase-shifting formulations, and may be adapted for injection of any desired injectable therapeutic to any desired tissue or organ.

[195] According to one particular embodiment of the present invention, an injection device is provided for intravitreal injection.

[196] Intravitreal injections have been used to administer pharmaceutically active agents to eyes to treat various eye conditions, such as macular degeneration, diabetic retinopathy, retinal vein occlusion and posterior uveitis. The active agents used are typically steroids, which may have long-term adverse systemic effects if administered systemically, and antibodies, such as anti-VEGF antibodies (such as bevacizumab, conbercept, aflibercept, pegaptanib and ranibzumab), which diffuse poorly from the blood system into eye tissues, and therefore intraocular, rather than systemic injection can be preferred in such instances.

[197] In performing intravitreal injections, care needs to be taken to ensure no, or minimal damage to other parts of the eye, including the lens, the retina, the ciliary bodies and muscles, the suspensory ligaments, or the cornea.

[198] The *pars plana* is a discrete area of the sclera. This area is a virtually concentric ring that is located between 2 mm and 4 mm away from the limbus, which in turn is 1-2 mm wide annular transition zone between the cornea and the sclera. This area is devoid of the inner retinal layer, is almost behind ciliary body and muscle, and allows direct access to the vitreous humour, avoiding the lens, making it the preferred target for intravitreal injection.

[199] Thus, and having reference to figures 1, 2, 5, 6, 8-11, 15, 24 and 25, as well as figures 35 to 43, 93 and 95, in one embodiment, an injector device according to the present invention comprises a sheath **170**, **170c** or **170d** (either as part of a needle hub **150**, **150c** or **150d** or as an extension of sleeve **70**, **70c** or **70d**), wherein sheath **170**, **170c** or **170d** has an eye-contacting surface at its distal end, or a pad **177**, **177c** or **172d** at its distal end that acts as an eye-contacting surface. The eye-contacting surface may be padded or have a rough surface to better hold its position on the eye during injection. In further embodiments the eye-contacting surface may be provided with features such as protrusions, ridges and/or other textural elements. In yet further embodiments, the contacting surface of the distal surface of sheath may include a combination of the aforementioned features or materials. Such materials and features may assist in holding the distal surface in position (for example in the correct injection position on the eye surface for intraocular injection) during the injection procedure, and may further assist the clinician in controlling or retaining the position of the eye in a desirable position during the injection. The eye-contacting surface may have an outer perimeter that defines a circle or modified circle, said surface being annular or in the form of a perforated concave disc, discoid or 3-dimensional annulus surface, with the needle defining the centre of said circle, although other shapes may be used. Where the eye-contacting surface is surface annular or in the form of a perforated concave disc, discoid surface or 3-dimensional annulus (needle **60/64** passes through the perforation), the diameter of the circle may be between 4 to 10

mm, more preferably between 6mm and 8mm, so as to provide a ready measurement of 2-5, preferably 3-4mm from the limbus to the pars plana, to ensure injection in the vitreous body of the eye. Where other eye-contacting surface shapes are used, this should still provide at least one eye-surface contacting edge that is 2-5mm, preferably 3-4mm from the needle to allow for correct positioning of the needle for intravitreal injection. Where the eye-contacting surface is a pad **177**, it may be made of a material that is softer or spongier, and/or is more capable of gripping the eye surface (to avoid movement of the sheath on the eye surface during the injection procedure) than the material of which sheath **170** or **170c** is comprised and may, for example, be made of silicone or rubber or an absorbent material. In certain embodiments sheath **170**, **170c** or **170d** for an intravitreal injection device according to the present invention may be substantially hollow cylindrical for most of its length, optionally with a frustoconical (narrowing) distal end. In use the eye contacting surface is placed on the sclera of the eye surface, with one edge of the eye-contacting surface being placed on the limbus (boundary of the white sclera and the cornea/iris) with the rest of the eye-contacting surface resting on the sclera (away from the cornea), thus ensuring that needle **60** or **64** enters the eye through the *pars plana* region, substantially reducing the risk of injury to major structures of the eye, including the retina, lens, and ciliary body. In certain embodiments the eye-contacting surface, such as pad **177** or **177c**, may have a pad **179** extending peripherally therefrom for applying pressure near the injection site after injection, to assist in stemming post wound leakage/reflux. A further advantage of pad **177** or **177c** is that it introduces significant asymmetry in sheath **170** or **170c** and cap **180**, such that a corresponding needle hub with cap **180** on can be readily screwed into barrel connector **46** or **210** or **210c** by applying axial rotational pressure on cap **180**. The sheath **170** or **170c** may also comprise a speculum for engaging an eyelid and keeping it away from the injection site during injection. The speculum may extend from the body of sheath **170** or **170c** with its eyelid contacting means being coterminous with eye-contacting surface **177** or **177c**.

[200] To avoid damage to the retina, intravitreal injection should ideally aim to deliver formulation to the centre of the vitreous cavity. Accordingly, in one embodiment, an intravitreal injection device according to the present invention may be configured to deliver pharmaceutical formulation at a depth of approximately 4 - 10mm, preferably 5-7mm. The injection depth at which plunger **80** or **80c** is released by the interaction between retention arm or toggle **120** or **120c** and restrainer **130** or **130c** (i.e., the injection depth at which injection is actuated) can be pre-determined based on: the size (i.e. proximal to distal length) of retention tabs **128** or **128c**, and the thickness of restrainer **130** or **130c**; the 'dead' space between the proximal surface of sleeve body **72** or **72c** and the bottom

surface of restrainer **130** or **130c**; and the 'dead' space between the eye-contacting surface and the tip of needle **60** when at rest.

[201] Injection devices according to the present invention may be disposable or be adapted to be used a number of times, either using replacement of formulation chambers or the device may be adapted for multiple injections from the same formulation chamber using replaceable, disposable needle hubs as described herein. In some embodiments, the injection device can be preassembled with formulation chamber and sterile packaged and ready for use without any further assembly. In other embodiments the injection device may be provided without needle hub (but with syringe cap in the barrel connector), and the needle hub provided separately, both sterile packaged. Certain injection devices according to the present invention are adapted for receiving standard formulation chambers or cartridges, which may be filled (including vacuum filled), sealed and sterilised in a facility skilled and experienced in such procedures, whereas the injector device and needle hub (if separate) may be manufactured at a different facility, skilled and experienced in those manufacturing procedures.

[202] In particular aspects, injection devices according to the present invention may be fully disposable or comprise a pre-assembled disposable single use elongated housing (including formulation chamber, sleeve, needle assembly, sheath) where the pre-assembled elongated housing is separable from an actuation housing that can be re-set, such as by a mechanism as described above and illustrated in Figures 99-100 and 108, to allow replacement of pre-assembled elongated housings (for example, one per patient). In such embodiments, the formulation chamber may be formed integrally with the elongated housing, or it may be adapted to have syringes or cartridges inserted into it. In such aspects the needle may be formed integrally with the elongated housing by, for example, being glued or overmoulded during formation of the elongated housing. Alternatively, the elongated housing may be adapted to have a needle assembly, such as a needle hub as described above, provided separately and attached. Where the elongated housing is adapted to receive a formulation cartridge (typically pre-filled), it may be advantageous to have the needle assembly (whether detachable or not) have a spring at its proximal end to urge the formulation chamber proximally and against the plunger (to assist in priming of the needle).

[203] In configurations where the elongated housing is adapted to receive pre-filled syringes adapted to have needle hubs attached thereto, then a spring between the syringe and the needle assembly may be replaced by a spring between the proximal end of the elongated housing and the proximal end or flange of the syringe. A spring in this proximal position would keep the syringe urged distally and in contact with the needle assembly, sealing between the two as the needle hub is

screwed on. As the needle hub is positioned on the distal end of the syringe the plunger contacts the stopper, pushing it forward, resulting in priming of the needle. Because the spring in proximal position keeps the needle hub in contact with the syringe tip, priming fluid is expelled through the needle and the system is primed when the needle hub is fully positioned.

[204] In one particular aspect of the present invention, there is provided an injection device comprising an elongated housing having a proximal end and a distal end, the proximal end being removably attached to an actuation mechanism, wherein:

the elongated housing defines an inner lumen between the proximal and distal ends which includes a formulation chamber formed integrally with the elongated housing, the formulation chamber also having corresponding proximal and distal ends, and having a stopper between its proximal and distal ends for retaining formulation in the formulation chamber;

the actuation mechanism having corresponding proximal and distal ends, and comprises an actuation housing with a proximal end connected to a dose delivery mechanism, and a distal end adapted for engaging the elongated housing, wherein the actuation mechanism includes a plunger, the distal end of the plunger engaging the stopper or being adapted to engage the stopper, and the plunger being in communication with a driving spring positioned between it and the proximal end of the actuation housing and which biases the plunger distally when the actuation mechanism is primed for injection, wherein the plunger is held in position against the bias by a toggle which has distal and proximal ends, and is connected to the plunger by a pivot point located between the distal and proximal ends, the toggle having an outwardly directed ledge positioned between the pivot point and the proximal end and adapted to engage an opposed inwardly directed ledge on or connected to the actuation housing to hold the plunger in a first unactuated position when the actuation mechanism is primed for injection, the proximal end of the toggle including a surface adapted to engage a complementary surface of a restrainer to hold the toggle in an unactuated position and thereby keep the outwardly directed ledge and opposed inwardly directed ledge in an engaged position, wherein the restrainer translates from an unactuated position or configuration to an actuated position or configuration when triggered, thereby allowing the toggle to deflect to an actuated position thereby uncoupling of the engagement between the outwardly directed ledge and opposed inwardly directed ledge and release of the plunger to move distally;

the elongated housing comprises a sleeve which is at least adapted to slide proximally between the elongated housing and the formulation chamber and is adapted to engage the restrainer such that proximal movement of the sleeve causes proximal movement of the restrainer;

the distal end of the elongated housing has a needle assembly comprising a needle that is glued or overmoulded in the distal end of the formulation chamber integrally formed with the

elongated housing and comprising a sheath, the sheath being adapted to engage the distal end of the sleeve, wherein the sheath is at least proximally slidable with respect to the needle so as to unsheath the needle during insertion of said needle into a subject and so as to slide the sleeve proximally, which results in proximal movement of the restrainer from the unactuated position to the actuated position, uncoupling of the engagement between the outwardly directed ledge and opposed inwardly directed ledge, and release of the plunger to move distally;

wherein the dose delivery mechanism comprises a first internal knob, a second, external dose setting knob, and a dose delivery housing adapted to sit on the proximal end of the actuation housing, wherein the proximal end of the plunger engages with the first knob via a thread with axial:longitudinal pitch X, the first knob engages with the second knob axially, but not longitudinally, and the second external dose setting knob engages with the dose delivery housing via a thread with axial:longitudinal pitch Y, wherein pitch Y is greater than pitch X, such that axial rotation of the second external dose setting knob results in the same degree of axial rotation as the first knob, but greater longitudinal travel of the second external dose setting knob compared to the first knob

wherein the actuator mechanism comprises a restrainer and retainer toggle which have interacting surfaces which are configured such that the toggle returns to its unactuated position when the plunger is moved proximally against the bias of the driving spring such that the first and second surfaces are again in an engaged position, and such that the restrainer returns to its unactuated position or configuration to again restrain the toggle in its unactuated position and ready to be triggered again.

[205] In another particular aspect of the present invention, there is provided an injection device comprising an elongated housing having a proximal end and a distal end, the proximal end being removably attached to an actuation mechanism, wherein:

the elongated housing defines an inner lumen between the proximal and distal ends which includes a separately formed formulation cartridge, the formulation chamber also having corresponding proximal and distal ends, and having a stopper between its proximal and distal ends for retaining formulation in the formulation cartridge;

the actuation mechanism having corresponding proximal and distal ends, and comprises an actuation housing with a proximal end connected to a dose delivery mechanism, and a distal end adapted for engaging the elongated housing, wherein the actuation mechanism includes a plunger, the distal end of the plunger engaging the stopper or being adapted to engage the stopper, and the plunger being in communication with a driving spring positioned between it and the proximal end of the actuation housing and which biases the plunger distally when the actuation mechanism is primed for injection, wherein the plunger is held in position against the bias by a toggle which has

distal and proximal ends, and is connected to the plunger by a pivot point located between the distal and proximal ends, the toggle having an outwardly directed ledge positioned between the pivot point and the proximal end and adapted to engage an opposed inwardly directed ledge on or connected to the actuation housing to hold the plunger in a first unactuated position when the actuation mechanism is primed for injection, the proximal end of the toggle including a surface adapted to engage a complementary surface of a restrainer to hold the toggle in an unactuated position and thereby keep the outwardly directed ledge and opposed inwardly directed ledge in an engaged position, wherein the restrainer translates from an unactuated position or configuration to an actuated position or configuration when triggered, thereby allowing the toggle to deflect to an actuated position thereby uncoupling of the engagement between the outwardly directed ledge and opposed inwardly directed ledge and release of the plunger to move distally;

the elongated housing comprises a sleeve which is at least adapted to slide proximally between the elongated housing and the formulation cartridge and is adapted to engage the restrainer such that proximal movement of the sleeve causes proximal movement of the restrainer;

the distal end of the elongated housing has a needle assembly integrally formed with the elongated housing comprising a needle or needles that extend distally and proximally from the needle assembly which also comprises a sheath, the sheath being adapted to engage the distal end of the sleeve, wherein the sheath is at least proximally slidable with respect to the needle so as to unsheath the needle during insertion of the needle into a subject and so as to slide the sleeve proximally, which results in proximal movement of the restrainer from the unactuated position to the actuated position, uncoupling of the engagement between the outwardly directed ledge and opposed inwardly directed ledge, and release of the plunger to move distally, wherein the needle assembly also comprises a spring at its proximal end and adapted to push proximally against the distal end of the formulation cartridge such that attachment of the needle assembly to the elongated housing results in piercing of the formulation cartridge septum and engagement of the plunger with the stopper and positive pressure between said plunger and said needle assembly resulting in a small amount of fluid being expelled from the formulation chamber through the needle, the needle being thereby primed with formulation;

wherein the dose delivery mechanism comprises a first internal knob, a second, external dose setting knob, and a dose delivery housing adapted to sit on the proximal end of the actuation housing, wherein the proximal end of the plunger engages with the first knob via a thread with axial:longitudinal pitch X, the first knob engages with the second knob axially, but not longitudinally, and the second external dose setting knob engages with the dose delivery housing via a thread with axial:longitudinal pitch Y, wherein pitch Y is greater than pitch X, such that axial rotation of the

second external dose setting knob results in the same degree of axial rotation as the first knob, but greater longitudinal travel of the second external dose setting knob compared to the first knob;

wherein the actuator mechanism comprises a restrainer and retainer toggle which have interacting surfaces which are configured such that the toggle returns to its unactuated position when the plunger is moved proximally against the bias of the driving spring such that the first and second surfaces are again in an engaged position, and such that the restrainer returns to its unactuated position or configuration to again restrain the toggle in its unactuated position and ready to be triggered again.

[206] In other aspects injection devices according to the present invention may be adapted for multiple injections from the same formulation chamber, be adapted for injection of different formulations or be fully re-usable (with the exception of formulation chamber and needles). In such aspects the elongated housing needs to be adapted to have needle assemblies, such as needle hubs as described above, replaceably attached thereto or to have syringes or cartridges, such as pre-filled syringes or cartridges, replaceably inserted therein – one per injection. In certain aspects such an elongated housing may be pre-assembled with a large volume formulation chamber (which may be integral or not) and be provided with an actuation mechanism that can be re-set, and allow for multiple injections from the one formulation chamber, replacing needle hubs only between injections. In other aspects the elongated housing is adapted to replaceably receive syringes, such as pre-filled syringes (which may have their own needles) or be adapted to receive formulation cartridges and have separately provided needle assemblies, such as needle hubs as described above, removably attached thereto.

[207] Components of the injection devices according to the present invention may be sterilizable by any method known in the art, such as by autoclaving, gamma radiation, ethylene oxide sterilization, etc.. In particular, needle assemblies, including needle hubs as described herein, as well as elongated housings (and components thereof) and plungers may be sterilizable and made of appropriate materials as known in the art. For example, while not intending to be limiting, springs, housings, and even plungers, retention arms/toggles intended to be re-used repeatedly may be made from stainless steel, although most components may be made from suitable plastics, such as polycarbonate (PC), acetonitrile butadiene styrene (ABS), PC/ABS combinations, acetal (polyoxymethylene), or nylon. Certain needle hub components, such as needle caps may be made from similar plastics or also polypropylene, polyisoprene or a thermoplastic elastomer. Needle valves, such as duck valves are typically made of silicone, and filters for use in needle hubs according to the invention, as described above, may be made of paper or other suitable polymeric insoluble

porous material. Formulation chambers of various sorts are typically made of glass (which may be spray or bake-coated with silicone) or thermostable plastics and comprise stoppers or septa which are typically made of a suitable rubber, such as chlorobutyl- or bromobutyl-rubbers. Where elongated housings are intended to have formulation chambers formed integrally, these may be made from, for example, cyclic olefin polymer.

[208] Additional aspects of the invention are also described as follows:

Aspect 1. An injection device comprising an elongated housing having a proximal end and a distal end, the proximal end comprising an actuation mechanism, wherein:

said elongated housing defines an inner lumen between said proximal and distal ends which is adapted to receive a formulation chamber and hold it in a fixed position relative to said actuation mechanism, said formulation chamber comprising or adapted to comprise an active agent for injection into a subject and said formulation chamber also comprising corresponding proximal and distal ends, and having stopper between its proximal and distal ends for retaining formulation in said formulation chamber and the distal end comprising a needle or being adapted to be in fluid communication with a needle.

said actuation mechanism also comprises corresponding proximal and distal ends, and comprises an actuation housing with a proximal end, and a distal end adapted for engaging said elongated housing, wherein said actuation mechanism comprises a plunger, the distal end of said plunger engaging said stopper or being adapted to engage said stopper, and the proximal end of said plunger being in communication with a first spring, said spring being positioned between said plunger and the proximal end of the actuation mechanism housing and being under stress when the actuation mechanism is primed for injection, wherein said plunger is held in position against said stress by retention arm or toggle, the bias force being directed outwardly from said plunger, said retention arm or toggle having plunger engaging means, wherein said retention arm or toggle engage said plunger when the actuation mechanism is primed for injection, said retention arm or toggle being held in plunger engaging position against the bias force by restrainer which translate from a restraining position or configuration to a releasing position or configuration when triggered.

Aspect 2. The injection device of Aspect 1, wherein the restrainer translates from a restraining position or configuration to a releasing position or configuration by a mechanism activated when a needle connected to the injection device reaching a desired injection depth.

Aspect 3. The injection device of Aspect 1 or Aspect 2, wherein the elongated housing also comprises a sleeve which is at least proximally slidable with respect to the elongated housing, and which slides proximally as a needle connected to the injection device is inserted into a subject.

Aspect 4. The injection device of Aspect 3, wherein the proximal movement of the sleeve results in proximal movement of the restrainer.

Aspect 5. The injection device of Aspect 4, wherein the restrainer are in restraining position when distal and in releasing position when proximal wherein, in use, said restrainer moves proximally as said sleeve is slid proximally relative to said elongated housing, thereby releasing the retention arm or toggle to deflect away from the plunger, allowing said first spring to drive said plunger and the stopper distally.

Aspect 6. The injection device of Aspect 5, wherein at least when in use, the distal end of the injection device comprises a sheath enshrouding at least a distal portion of a needle assembly in fluid communication with said formulation chamber, said sheath being either an integral part of said sleeve or being adapted to engage the distal end of said sleeve and being adapted to slide between said elongated housing and said formulation chamber, and wherein said sheath is at least proximally slidable with respect to the needle so as to unsheath the needle during insertion of said needle into a subject and so as to move said sleeve proximally, resulting in proximal movement of the retaining means to a retention arm or toggle-releasing position.

Aspect 7. The injection device of Aspect 6, wherein said sleeve and sheath are held in a needle enshrouding position by a second spring stressed between the actuation housing and the sleeve, which is adapted to engage said second spring.

Aspect 8. The injection device of Aspect 6 wherein said sheath comprises biasing means stressed between a distal portion of the sheath and the needle assembly to ensure the sheath covers the needle tip.

Aspect 9. The injection device of any one of Aspects 6 to 8, wherein said retention arm or toggle, once released, is adapted to stop said sleeve and sheath from proximal movement once said sleeve and sheath have returned to a needle-enshrouding position.

Aspect 10. The injection device of any one of Aspects 1 to 9, wherein said retention arm or toggle comprise at least one biased arm, said at least one biased arm being connected at one end to the proximal end of said actuation mechanism housing, the other end of said at least one biased arm

comprising an inwardly directed ledge adapted to engage a complementary outwardly directed ledge on said plunger, said outwardly directed ledge being optionally formed as a groove in or a ridge on said plunger.

Aspect 11. The injection device of any one of Aspects 1 to 10, wherein said actuation mechanism housing and said elongated housing are detachable from one another to allow placement, removal or replacement of formulation chamber(s) into or from said elongated housing.

Aspect 12. The injection device of Aspect 11 wherein said formulation chamber is pre-filled, optionally vacuum or voidless filled.

Aspect 13. The injection device of Aspect 12, wherein engagement of said plunger with said stopper and placement of the formulation chamber in said elongated housing and connection of said actuation housing to said elongated housing results in positive pressure within said formulation chamber or actuation mechanism.

Aspect 14. The injection device of Aspect 13, wherein when a needle is placed in fluid communication with the distal end of said formulation chamber, said positive pressure results in a small amount of fluid being expelled from the formulation chamber through said needle, the needle being thereby filled with formulation.

Aspect 15. The injection device of any one of Aspects 1 to 14, wherein the distal end of said formulation chamber is adapted to have a needle assembly attached thereto.

Aspect 16. The injection device of any one of Aspects 1 to 14, wherein the distal end of said elongated housing is adapted to have a needle assembly attached thereto and allow fluid communication between said formulation chamber and said needle.

Aspect 17. The injection device of Aspect 15 or Aspect 16 wherein said needle assembly is attached to the distal end of said formulation chamber or said elongated housing by means of a screw or a Luer lock mechanism.

Aspect 18. The injection device of any one of Aspects 1 to 14, wherein said needle forms an integral part of at least said formulation chamber.

Aspect 19. The injection device of any one of Aspects 1 to 14, wherein said needle forms an integral part of said elongated housing.

Aspect 20. The injection device of any one of Aspects 1 to 17, which comprises:
an elongated housing comprising an inner sleeve said housing and sleeve defining a lumen adapted to receive a formulation chamber;
an actuation mechanism housing detachably connectable to the proximal end of said elongated housing; and optionally
a needle assembly detachably connectable to the distal end of said elongated housing or said formulation chamber, said needle assembly comprising a sheath which is adapted to engage the distal end of said sleeve and being adapted to slide between said elongated housing and said formulation chamber, and wherein said sheath is at least proximally slidable with respect to the needle so as to unsheath the needle during insertion of said needle into a subject and so as to slide said sleeve proximally, resulting in proximal movement of said restrainer to a retention arm or toggle releasing position.

Aspect 21. The injection device of any one of Aspects 1 to 20, wherein said actuation housing comprises proximal and distal portions engaged via adjustable means, such that the distance between the proximal and distal ends of said actuation housing, and therefore the allowable travel distance of said plunger, can be set to a specified distance, thereby allowing setting of a defined volume of formulation to be dispensed on actuation of the injection device.

Aspect 22. The injection device of any one of Aspects 1 to 20, wherein said plunger has a proximal end that extends proximally beyond the actuation housing and engages with a cap via adjustable means, such that the distance between the cap and the actuation housing, and therefore the allowable travel distance of said plunger can be set to a specified distance, thereby allowing setting of a defined volume of formulation to be dispensed on actuation of the injection device.

Aspect 23. The injection device of any one of Aspects 1 to 22 which comprises a mechanism that signals successful actuation of the device via audible, tactile or visual means.

Aspect 24. The injection device of any one of Aspects 1 to 23 which is for intravitreal injection and comprises a sheath enshrouding at least a distal portion of a needle assembly in fluid communication with said formulation chamber, said sheath being either an integral part of said sleeve or being adapted to engage the distal end of said sleeve and being adapted to slide between said elongated housing and said formulation chamber, and wherein said sheath is at least proximally slidable with respect to the needle so as to unsheath the needle during insertion of said needle into a subject and so as to slide said sleeve, resulting in proximal movement of the sleeve against said

restrainer and movement of said restrainer to a retention arm or toggle-releasing position, wherein said sheath has a distal eye-contacting surface.

Aspect 25. The injection device of Aspect 24, wherein said eye-contacting surface has an outer perimeter that defines a circle or modified circle, said surface being annular or in the form of a perforated concave disc, discoid or 3-dimensional annulus surface, with the needle defining the centre of said circle, and wherein the diameter of said circle is between 4 to 10 mm, optionally between 6mm and 8mm.

Aspect 26. The injection device of Aspect 24 or Aspect 25 wherein said sheath comprises an external pad which is substantially coterminous with said eye-contacting surface for applying pressure next to the injection site after injection.

Aspect 27. A needle hub for attachment to an injection device according to any one of Aspects 12 to 17 or 20 comprising a needle and a body, said body comprising a proximal end having the proximal end of the needle protruding proximally from it and a main body with the injection end of the needle protruding distally from it, the proximal end of said body being adapted for engagement with said elongated housing or said formulation chamber, the needle hub also comprising a sheath enshrining the needle and main body, the proximal end of the sheath being adapted to: retain the main body of the needle assembly within the sheath; to engage the sleeve of said injection device; and to fit and slide within the elongated housing, said needle hub optionally also comprising a cap which fully enshrouds at least the distal end of said needle hub.

Aspect 28. A needle hub for attachment to an injection device according to any one of Aspects 12 to 17 or 20 comprising a main body having a proximal body and a distal body, the proximal body being adapted for engagement with the elongated housing or the formulation chamber and a proximal needle extending proximally from it, the distal body comprising a distal needle extending distally from it, the proximal and distal bodies being adapted to connect together with a filter enclosed between them and between the two needles, the needle hub also comprising a sheath enshrining the needle and main body, the proximal end of the sheath being adapted to: retain the main body of the needle assembly within the sheath when not in use; to engage the sleeve of said injection device; and to fit and slide within the elongated housing.

Aspect 29. The needle hub of Aspect 28, wherein the proximal needle has a larger gauge than the distal needle.

Aspect 30. The needle hub of Aspect 29, wherein the distal needle has a gauge of 25 (approximately 0.5mm outer diameter) or finer, preferably gauge 27 (approximately 0.4mm outer diameter) or finer.

Aspect 31. The needle hub of any one of Aspects 27 to 30 wherein said sheath is substantially cylindrical for most of its length, with a frustoconical distal end.

Aspect 32. The needle hub of any one of Aspects 27 to 31 which is for intravitreal injection and has a distal eye-contacting surface.

Aspect 33. The needle hub of Aspect 32, wherein said eye-contacting surface has an outer perimeter that defines a circle or modified circle, said surface being annular or in the form of a perforated concave disc, discoid or 3-dimensional annulus surface, with the needle defining the centre of said circle, and wherein the diameter of said circle is between 4 to 10 mm, optionally between 6mm and 8mm.

Aspect 34. The needle hub of Aspect 32 or Aspect 33, which comprises a sheath which has an external pad which is substantially coterminous with the eye-contacting surface for applying pressure next to the injection site after injection.

Aspect 35. The needle hub of any one of Aspects 27 to 34 comprising a cap when not in use, said cap being adapted to fully enshroud at least the distal end of said needle hub, optionally also including means to ensure that said cap does not rotate axially with respect to said main body when connecting the needle hub to said injection device.

Aspect 36. A delivery device configured to deliver a medicinal agent to an area of anatomy of a patient, the delivery device having:

an elongated housing having a proximal end and a distal end and defining an inner lumen extending between the proximal end and the distal end;
at least one actuation mechanism, disposed within the inner lumen of the proximal end of the elongated housing, further having corresponding proximal and distal ends, at least one plunger, and
at least one retention means configured to retain the at least one actuation mechanism in a first primed configuration, wherein the at least one retention means is in a first position corresponding to the first primed configuration wherein the at least one retention means restricts the at least one plunger from moving in at least one axis of motion, and further wherein the at least one retention means is configured to be movable to a second position corresponding to a second delivery

configuration further wherein movement of the at least one plunger is no longer restricted by the at least one retention means;

at least one chamber configured to contain a medicinal agent, having corresponding proximal and distal ends;

at least one needle hub, coupled to the distal end of the elongated housing, having at least one needle configured to deliver the medicinal agent to an anatomical area of the patient, and configured to be coupled to the at least one chamber such that the at least one needle is in fluid communication with the at least one chamber, and further having at least one needle sheath, which is slidably movable with respect to an axis substantially normal to the anatomical area of a patient, wherein this movement is capable of moving the at least one needle sheath between a first non-retracted configuration and a second retracted configuration;

at least one dose selection mechanism, coupled to the proximal end of the elongated housing and to the proximal end of the at least one actuation mechanism, wherein the at least one dose selection mechanism is configured to select a desired dose of medicinal agent;

and

at least one trigger mechanism having a first unactuated position and a second actuated position, configured to trigger a transition of the at least one actuation mechanism from a first primed configuration to a second delivery configuration and further configured to be in communication at least one actuation mechanism;

wherein the transition of the at least one trigger mechanism from a first unactuated position to a second actuated position triggers the movement of the at least one retention means from its first position to its second position, triggering movement of the at least one actuation mechanism as determined by the at least one dose selection mechanism, and triggering expulsion of a correlated desired dose of medicinal agent from the at least one chamber through the at least one needle into the anatomical area of the patient.

Aspect 37. The delivery device of Aspect 36, wherein the at least one trigger mechanism is induced to move from the first unactuated position to a second actuated position by pressing the at least one needle sheath of the at least one needle hub to the anatomical area to be injected.

Aspect 38. The delivery device of Aspect 36 or 37, wherein the at least one chamber further has at least one stopper located at at least one of its proximal or distal end.

Aspect 39. The delivery device of Aspect 38, wherein the at least one stopper is disposed at both the proximal and distal ends of the at least one chamber.

Aspect 40. The delivery device of Aspect 38 or 39, wherein the at least one stopper disposed at the proximal end is coupled to the at least one plunger.

Aspect 41. The delivery device of any of Aspects 38-40 wherein the at least one needle of the needle hub is configured to extend through the at least one stopper disposed at the distal end to facilitate fluid communication between the at least one chamber and the at least one needle.

Aspect 42. The delivery device of Aspect 41, wherein the needle hub comprises at least two needles.

Aspect 43. The delivery device of Aspect 36, wherein the dose selection mechanism is configured to select a distance between the at least one dose selection mechanism and a housing, thereby providing a limit on the distance traveled by the at least one plunger of the actuation mechanism to deliver a correlated dose of medicinal agent.

Aspect 44. The delivery device of any of claims 36-43, wherein the dose selection mechanism is configured to select a discrete dose quantity.

Aspect 45. The delivery device of Aspect 44, wherein the at least one dose selection mechanism further comprises:

- at least one knob having an interior surface and at least one recess disposed on said interior surface and configured to be rotatable about a longitudinal axis of the delivery device;

- and

- at least one housing coupled to the at least one knob, having at least one ledge positioned distally relative to an inferior aspect of the at least one knob, and further having least one finger configured to fit within a space defined by the interior surface of the at least one knob, wherein the at least one finger further has at least one protrusion corresponding to a set distance from the at least one ledge and configured to be received by the at least one recess of the at least one knob;

- and

- wherein the at least one knob is configured to be rotated until the at least one finger of the housing is received in the at least one recess of the at least one knob, which additionally moves the knob in an axial direction away from the at least one ledge of the at least one housing and creating a distance between the inferior aspect of the knob and the at least one ledge of the housing corresponding to a dose of medicinal agent to be delivered.

Aspect 46. The delivery device of any of Aspects 36-45, wherein the at least one actuation mechanism further comprises:

at least one needle sheath, which is slidably movable with respect to an axis substantially normal to the anatomical area of a patient, this slidable movement capable of moving the at least one needle sheath between a first non-retracted configuration and a second retracted configuration;

at least one barrel sheath having a proximal end and a distal end, wherein at least one spring is disposed at the proximal end and coupled to the at least one needle sheath at the distal end, such that the movement of needle sheath from its first non-retracted configuration to its second retracted configuration induces a corresponding movement of the at least one barrel sheath, thereby compressing the at least one spring of the at least one barrel spring;

at least one plunger having a proximal end and a distal end, having at least one spring disposed adjacent to a collar disposed at the proximal end of the at least one plunger and extending into an at least one chamber of a delivery device at its distal end, the at least one plunger and the at least one chamber further extending through the at least one barrel sheath;

at least one retention arm, coupled to the at least one plunger at a point in between its proximal end and distal end, having a first unactuated position and a second actuated position; and

at least one locking ring coupled to the at least one plunger such that it is slidably movable along an axis substantially normal to the anatomical area of a patient, having a first position configured to restrict movement of the at least one retention arm, thereby retaining the at least one retention arm in its first unactuated position, and further configured to contact the proximal end of the at least one barrel sheath, wherein such contact slidably moves the at least one locking ring into a second position such that it bears against the collar disposed on the proximal end of the at least one plunger such that the at least one spring disposed at the proximal end of the at least one plunger is compressed, and further wherein movement of the at least one retention arm is unrestricted such that it can move into its second actuated position; and Wherein the movement of the at least one retention arm from its first unactuated position to its second actuated position allows the at least one spring of the proximal end of the at least one plunger to decompress, subjecting the collar of the at least one plunger to a force, thereby moving the distal end of the at least one plunger through the chamber to expel the medicinal agent from the delivery device.

Aspect 47. The delivery device of Aspects 36-46, wherein the dose selection mechanism further incorporates at least one indicator configured to indicate the desired dose.

Aspect 48. The delivery device of Aspect 47, wherein the at least one indicator is at least one of a visual indicator of the dose disposed on an exterior portion of the delivery device, a haptic

indicator, an auditory indicator, or an electronic signal configured to interface with an application on a separate electronic device.

Aspect 49. The delivery device of any of Aspects 36-48, wherein the needle sheath is unable to be retracted again after a dose is delivered.

Aspect 50. The delivery device of any of Aspects 36-49, wherein the needle hub is configured to be removably attached to the housing.

Aspect 51. The delivery device of any of Aspects 36-50, wherein the at least one chamber is a separable cartridge.

Aspect 52. The delivery device of any of Aspects 36-51, wherein the delivery device is configured to be used with higher viscosity fluids.

Aspect 53. The delivery device of any of claims 36-52, wherein the device is configured for use in ophthalmological procedures.

Aspect 54. A delivery device configured to deliver a medicinal agent to an area of anatomy of a patient, the delivery device having:

- an elongated housing having a proximal end and a distal end and defining an inner lumen extending between the proximal end and the distal end;

- at least one chamber configured to contain a medicinal agent, disposed within the inner lumen of the elongated housing having corresponding proximal and distal ends;

- at least one needle hub, coupled to the distal end of the elongated housing, having at least one needle configured to deliver the medicinal agent to the anatomical area of the patient, and configured to be coupled to the at least one chamber such that the at least one needle is in fluid communication with the at least one chamber, and further having at least one needle sheath, which is slidably movable with respect to an axis substantially normal to an anatomical area of a patient, wherein this movement is capable of moving the at least one needle sheath between a first non-retracted configuration and a second retracted configuration;

- at least one barrel sheath disposed within the inner lumen of the elongated housing and around the at least one chamber, having a proximal end and a distal end, wherein at least one spring is disposed at the proximal end and coupled to the at least one needle sheath at the distal end, such that the movement of needle sheath from its first non-retracted configuration to its second retracted configuration induces a corresponding axial movement of the at least one barrel sheath, thereby compressing the at least one spring of the at least one barrel spring;

at least one plunger having a proximal end and a distal end, having at least one spring positioned adjacent to a collar disposed at the proximal end of the at least one plunger and extending into an at least one chamber of a delivery device at its distal end, the at least one plunger and the at least one chamber further extending through the at least one barrel sheath;

at least one retention arm, coupled to the at least one plunger at a point in between its proximal end and distal end, having a first unactuated position and a second actuated position;

at least one locking ring coupled to the at least one plunger such that it is slidably movable along an axis substantially normal to the anatomical area of a patient, having a first position configured to restrict movement of the at least one retention arm, thereby retaining the at least one retention arm in its first unactuated position, and further configured to contact the proximal end of the at least one barrel sheath, wherein such contact slidably moves the at least one locking ring into a second position such that it bears against the collar disposed on the proximal end of the at least one plunger such that the at least one spring disposed at the proximal end of the at least one plunger is compressed, and further wherein movement of the at least one retention arm is unrestricted such that it can move into its second actuated position;

at least one knob coupled to the proximal end of the at least one plunger having an interior surface and at least one recess disposed on said interior surface and configured to be rotatable about a longitudinal axis of the delivery device;

at least one dosing housing coupled to the at least one knob and disposed about the at least one plunger, having at least one ledge positioned distally relative to an inferior aspect of the at least one knob;

wherein the at least one knob is configured such that, when rotated, it additionally moves the knob in an axial direction away from the at least one ledge of the at least one dosing housing and creates a distance between the inferior aspect of the knob and the at least one ledge of the dosing housing corresponding to a dose of medicinal agent to be delivered; and further wherein the movement of the at least one retention arm from its first unactuated position to its second actuated position allows the at least one spring of the proximal end of the at least one plunger to decompress, subjecting the collar of the at least one plunger to a force, thereby moving the distal end of the at least one plunger through the chamber a distance corresponding to the distance between the at least one ledge of the at least one housing and the inferior edge of the at least one knob to expel a corresponding dose of the medicinal agent through the at least one needle into the area of anatomy of the patient.

Aspect 55. The delivery device of Aspect 54, wherein the at least one chamber further has at least one stopper located at at least one of its proximal or distal end.

Aspect 56. The delivery device of Aspect 55, wherein the at least one stopper is disposed at both the proximal and distal ends of the at least one chamber.

Aspect 57. The delivery device of Aspect 55 or 56, wherein the at least one stopper disposed at the proximal end is coupled to the at least one plunger.

Aspect 58. The delivery device of any of Aspects 56-57 wherein the at least one needle of the needle hub is configured to extend through the at least one stopper disposed at the distal end to facilitate fluid communication between the at least one chamber and the at least one needle.

Aspect 59. The delivery device of Aspect 58, wherein the needle hub comprises at least two needles.

Aspect 60. The delivery device of any of Aspects 54-59, wherein the delivery device is configured to select a discrete dose quantity.

Aspect 61. The delivery device of Aspect 60, wherein the interior surface of the at least one knob has at least one recess, and the at least one housing has at least one finger configured to fit within a space defined by the interior surface of the at least one knob wherein the at least one finger further has at least one protrusion corresponding to a set distance from the at least one ledge and configured to be received by the at least one recess of the at least one knob; and

wherein the at least one knob is configured to be rotated until the at least one finger of the housing is received in the at least one recess of the at least one knob, which additionally moves the knob in an axial direction away from the at least one ledge of the at least one housing and creating a distance between the inferior edge of the knob and the at least one ledge of the housing corresponding to a dose of medicinal agent to be delivered.

Aspect 62. The delivery device of Aspects 54-61, wherein the delivery device further incorporates at least one indicator configured to indicate the desired dose.

Aspect 63. The delivery device of Aspects 54-62, wherein the at least one indicator is at least one of a visual indicator of the dose disposed on an exterior portion of the delivery device, a haptic indicator, an auditory indicator, or an electronic signal configured to interface with an application on a separate electronic device.

Aspect 64. The delivery device of any of Aspects 54-63, wherein the needle sheath is unable to be retracted again after a dose is delivered.

Aspect 65. The delivery device of any of Aspects 54-64, wherein the needle hub is configured to be removably attached to the housing.

Aspect 66. The delivery device of any of Aspects 54-65, wherein the at least one chamber is a separable cartridge.

Aspect 67. The delivery device of any of Aspects 54-66, wherein the delivery device is configured to be used with higher viscosity fluids.

Aspect 68. The delivery device of any of Aspects 54-67, wherein the device is configured for use in ophthalmological procedures.

Aspect 69. An actuation mechanism configured to deliver a selected dose of a medicinal agent from at least one chamber of a delivery device, through a delivery device to an anatomical area of a patient, the actuation mechanism comprising:

- at least one needle sheath, which is slidably movable with respect to an axis substantially normal to the anatomical area of a patient, this slidable movement capable of moving the at least one needle sheath between a first non-retracted configuration and a second retracted configuration;

- at least one barrel sheath having a proximal end and a distal end, wherein at least one spring is disposed at the proximal end and coupled to the at least one needle sheath at the distal end, such that the movement of needle sheath from its first non-retracted configuration to its second retracted configuration induces a corresponding movement of the at least one barrel sheath, thereby compressing the at least one spring of the at least one barrel spring;

- at least one plunger having a proximal end and a distal end, having at least one spring disposed adjacent to a collar disposed at the proximal end of the at least one plunger and extending into an at least one chamber of a delivery device at its distal end, the at least one plunger and the at least one chamber further extending through the at least one barrel sheath;

- at least one retention arm, coupled to the at least one plunger at a point in between its proximal end and distal end, having a first unactuated position and a second actuated position;

and

- at least one locking ring coupled to the at least one plunger such that it is slidably movable along an axis substantially normal to the anatomical area of a patient, having a first position configured to restrict movement of the at least one retention arm, thereby retaining the at least one retention arm in its first unactuated position, and further configured to contact the proximal end of the at least one barrel sheath, wherein such contact slidably moves the at least one locking ring into a second position such that it bears against the collar disposed on the proximal end of the at least one

plunger such that the at least one spring disposed at the proximal end of the at least one plunger is compressed, and further wherein movement of the at least one retention arm is unrestricted such that it can move into its second actuated position;

wherein the movement of the at least one retention arm from its first unactuated position to its second actuated position allows the at least one spring of the proximal end of the at least one plunger to decompress, subjecting the collar of the at least one plunger to a force, thereby moving the distal end of the at least one plunger through the chamber to expel the medicinal agent from the delivery device.

Aspect 70. A dosing mechanism configured to select an appropriate dose of medicinal agent for delivery of a medicinal agent to an area of anatomy of a patient by a delivery device, the dosing mechanism comprising:

at least one knob having an interior surface and at least one recess disposed on said interior surface and configured to be rotatable about a longitudinal axis of the delivery device;

and

at least one housing coupled to the at least one knob, having at least one ledge positioned distally relative to an inferior aspect of the at least one knob, and further having least one finger configured to fit within a space defined by the interior surface of the at least one knob, wherein the at least one finger further has at least one protrusion corresponding to a set distance from the at least one ledge and configured to be received by the at least one recess of the at least one knob;

wherein the at least one knob is configured to be rotated until the at least one finger of the housing is received in the at least one recess of the at least one knob, which additionally moves the knob in an axial direction away from the at least one ledge of the at least one housing and creating a distance between the inferior aspect of the knob and the at least one ledge of the housing corresponding to a dose of medicinal agent to be delivered.

Aspect 71. A system for administering delivery of a medicinal agent to a patient, the system comprising:

a delivery device according to any of Aspects 1-70;

an electronic device; and

an application configured to track and store information related to the delivery of care.

Aspect 72. A method of delivering a dose of a medicinal agent to an area of anatomy of a patient using a delivery device, the method comprising the following steps:

a. Removing a needle cover from the delivery device;

- b. Selecting a dose of the medicinal agent by rotating a knob positioned at the proximal end of the delivery device, thereby creating a distance between the knob and a ledge disposed on the housing of the delivery device;
- c. Positioning a needle sheath adjacent to a surface of the area of anatomy of the patient;
- d. Depressing the delivery device such that the needle sheath retracts into the body of the delivery device, exposing the needle;
- e. Inserting the needle a depth determined by the retraction of the needle sheath into the body of the delivery device;
- f. Waiting for the device to deliver the medicinal agent, using the diminishing distance between the knob and the ledge as an indicator of progress;
- g. Removing the needle from the anatomy of the patient, thereby allowing the needle sheath to return to its original, non-retracted position.

[209] Preferred forms of the present invention will now be described, by way of example only, with reference to the following examples, including comparative data, and which are not to be taken to be limiting to the scope or spirit of the invention in any way.

Examples

Example 1 – Methods and Materials

[210] For dose delivery accuracy and dose triggering force experiments data were derived by filling formulation cartridges with water or calibrated oil.

[211] Injection devices according to the fifth embodiment, with delivery dose mechanisms as illustrated in Figure 98, were used for dose delivery accuracy experiments, with three variants – IVAI 5.1, 5.2 and 5.3 - which had differences in the thread between the inner knob and plunger such that IVAI 5.1 required one full turn of the knob to deliver 100µL, IVAI 5.2 required two full, and IVAI 5.3 required 2 full turns to deliver 100µL turns of the knob to deliver 20µL. Driving springs for all devices were the same (Century Springs A89, 35.05mm in length, 1.61 N per mm) and provided a force of 34.7 N when assembled.

[212] Injection devices according to the fifth embodiment with either dose delivery mechanisms as illustrated in Figure 98 or as illustrated in Figure 71 were used for the triggering force experiments.

[213] The devices were assembled and the needles primed when the needle hubs were attached. Desired doses were then selected by turning external knob 500f to the appropriate point. When

ready for testing, devices were then placed into the upper jaw of a Universal (Mechanical) Testing Machine (UTM), and pre-weighed cup receptacles placed in the lower jaw. Devices were then brought down at a constant speed until the needle sheath contact the solid lid of the cup, with the needle aligned to protrude through a hole in the lid. The UTM continued to push the needle hub into the lid as a clinician would push the device into the sclera of a patient until devices were triggered, at which time the fluid is expelled from the cartridge into the cup, through the needles. The upper jaw with devices then moved up away from cup, allowing the needle sheath to cover the distal needle once more and result in “lock out” (whereby the sheath and sleeve could no longer slide proximally). In a further test devices were brought back down to verify successful “lock out”.

[214] The weight of the fluid and the cup post injection was determined, and subtracting the pre-injection weight of the cup allowed determination of the dose delivered and accuracy, relative to what was selected on the external knob. The upper jaw of the UTM has a force sensor that can measure the force applied to the device during the entire travel of the device in the UTM, allowing identification of the moment of triggering, and force applied at that time. The results obtained are a good representation of the results that would be obtained by a user, as the user has no input into the delivery of the fluid (other than dose setting which is part of this test protocol) and force with which the device activates as this is all automated.

Example 2 – Dose Accuracy

[215] The results obtained are shown in Table 1.

Table 1

	Injector and Formulation				
	IVAI 5.3 100cP	IVAI 5.1 1cP	IVAI 5.1 100cP	IVAI 5.2 1cP	IVAI 5.2 100cP
Dose Set Target(μL)	10	50	50	50	50
Fluid viscosity	100cP	1cP	100cP	1cP	100cP
Average dose delivered (μL)	10.45	51.35	53.38	51.00	51.17
Standard deviation (μL)	0.56	1.60	2.79	0.14	1.00

[216] By comparison, values which can be found in the literature show significantly poorer dose accuracy and consistency. Tables 2 to 4 show data from three different reports on injection reproducibility: Goldberg R.A. (Charters L, *Ophthalmology Times*, 13 November 2021, reporting on presentation by R.A. Goldberg at the American Academy of Ophthalmology 2021 annual meeting in New Orleans); Dingerkus *et al* (Dingerkus VLS *et al* (2002) *Sci Rep.* **12**(1):18136); and Guest *et al* (Guest JM *et al* (2022), *Int J Retina Vitreous*, **8**(1):27).

Table 2

	Injector and Formulation		
	PFS Goldberg-1 (Base to Prox Edge)	PFS Goldberg-2 (Base to Dist Edge)	PFS Goldberg-3 (Tip to Dist Edge)
Dose Set Target (μL)	50	50	50
Fluid viscosity	1cP (Purified water)	1cP (Purified water)	1cP (Purified water)
Average dose delivered (μL)	54.8	78.9	109.7
Standard deviation (μL)	5.7	5.7	3.4

Table 3

	Injector and Formulation			
	PFS Dingerkus-1 (NVnP)	PFS Dingerkus-2 (NVwP)	PFS Dingerkus-3 (HVnP)	PFS Dingerkus-4 (HVwP)
Dose Set Target (μL)	50	50	50	50
Fluid viscosity	Aflibercept (ca. 12cP)	Aflibercept (ca. 12cP)	Aflibercept (ca. 12cP)	Aflibercept (ca. 12cP)
Average dose delivered (μL)	56.06	70.69	74.22	81.63
Standard deviation (μL)	10.32	4.56	7.41	3.67

[217] The Goldberg-1, 2, and 3 values are results for using a Prefilled Syringe (PFS) in different ways, where they show that depending on how you align the plunger/stopper with the dose mark on the glass, can greatly affect your dose accuracy. Dingerkus-1, 2, 3 and 4 values were for similar tests, but also show how pressing hard on the plunger/stopper at the end of the injection also affects the dose accuracy. Table 4 shows values extrapolated from the Guest publication for pre-filled syringes (PFS), Luer-lock syringes, and similar devices.

[218] Table 4

	Injector and Formulation		
	PFS - Guest	Luer Syringe - Guest	Similar Devices
	PFS Guest	BD Luer Syringe Guest	MDS Congruence
Dose Set Target (μL)	50	50	50
Fluid viscosity	Aflibercept (ca. 12cP)	Aflibercept (ca. 12cP)	N/A
Average dose delivered (μL)	74.22	53.42	N/A
Standard deviation (μL)	15.87	4.61	2.5

[219] As can be seen from the data, dose accuracy and variability (standard deviation) for the injectors according to the present invention is significantly better than for the devices tested in the Goldberg, Dingerkus and Guest articles.

Example 3 – Trigger Force

[220] Average trigger forces for Injection devices according to the fifth embodiment when dispensing water (1cP viscosity) or calibrated oil (100cP viscosity) with dose delivery mechanisms as illustrated in Figure 98 were 1.90 N (with a standard deviation of 0.39 N), with little difference between the triggering forces when delivering water or calibrated oil. Average trigger forces for Injection devices according to the fifth embodiment when dispensing water (1cP viscosity) or calibrated oil (100cP viscosity) with dose delivery mechanisms as illustrated in Figure 71 (and having the same driving spring as IVAI 5.1, 5.2 and 5.3) were also very low, being 1.01 N for delivery of water (1cP viscosity) and 1.29 N for delivery of calibrated oil (100cP viscosity).

[221] It will be appreciated that, although specific embodiments of the invention have been described herein for the purpose of illustration, various modifications may be made without deviating from the spirit and scope of the invention as defined in the following claims.

Claims:

1. An injection device comprising an elongated housing having a proximal end and a distal end, the proximal end comprising an actuation mechanism, wherein:

said elongated housing defines an inner lumen between said proximal and distal ends which is adapted to receive and hold a formulation chamber relative to said actuation mechanism, said formulation chamber also having corresponding proximal and distal ends, and having a stopper between its proximal and distal ends for retaining formulation in said formulation chamber;

said actuation mechanism having corresponding proximal and distal ends, and comprises an actuation housing with a proximal end, and a distal end adapted for engaging said elongated housing, wherein said actuation mechanism includes a plunger, the distal end of said plunger engaging said stopper or being adapted to engage said stopper, said plunger being in communication with at least one driving spring which biases the plunger distally when the actuation mechanism is primed for injection,

wherein said plunger is held in position against said bias by at least one retention arm or toggle having at least one first surface adapted to engage an opposed complementary second surface to hold said plunger in a first unactuated position when the actuation mechanism is primed for injection, the first and second surfaces being held in an engaged position by a restrainer which translates from an unactuated position or configuration to an actuated position or configuration when triggered, thereby allowing uncoupling of the engagement between the first and second surfaces and release of the plunger to move distally.

2. The injection device of claim 1, wherein the restrainer translates from the unactuated position or configuration to the actuated position or configuration by a trigger mechanism activated when a needle connected to the injection device reaches a desired injection depth.

3. The injection device of claim 1 or claim 2, wherein the elongated housing includes a sleeve which is at least proximally slidable between the elongated housing and the formulation chamber and is adapted to engage the restrainer such that proximal movement of the sleeve causes proximal movement of the restrainer, and wherein operatively, insertion of a needle connected to the injection device into a surface results in the sleeve sliding proximally and, as a result, the restrainer moves proximally to the actuated position or configuration.

4. The injection device of claim 3, wherein the restrainer is in the unactuated position when distal and in the actuated position when proximal, so that operatively, the restrainer moves proximally as the sleeve is slid proximally relative to the elongated housing, thereby releasing the

retention arm or toggle to uncouple the first and second surfaces allowing said at least one driving spring to drive the plunger and the stopper distally.

5. The injection device of any one of claims 1 to 4, comprising a retention toggle which has distal and proximal ends, and is connected to the plunger by a pivot point located between said distal and proximal ends.

6. The injection device of claim 5, wherein said first surface of the toggle is in the form of an outwardly directed ledge adapted to engage an opposed complementary second surface in the form of an inwardly directed ledge on or connected to the actuation housing, the proximal end of the toggle including a surface adapted to engage a complementary surface of the restrainer.

7. The injection device of claim 6 wherein the outwardly directed ledge is positioned between the pivot point and the proximal end of the toggle.

8. The injection device of claim 6 or claim 7, wherein the triggering force required to allow uncoupling of the engagement between the first and second surfaces and release of the plunger to move distally is inversely proportional to a value a/b , wherein a is the distance between the proximal end of the toggle and the pivot point and b is the distance between the first surface and the pivot point, allowing regulation of the triggering force by regulation of the value a/b .

9. The injection device of claim 8 for use in an injection indicating low triggering force and configured such that b is substantially smaller than a .

10. The injection device of claim 8 wherein the value of a divided by b is greater than or equal to 1.

11. The injection device of any one of claims 1 to 10, wherein the elongated housing comprises a sleeve which is at least proximally slidable between the elongated housing and the formulation chamber and is adapted to engage the restrainer such that proximal movement of the sleeve causes proximal movement of the restrainer and wherein, operatively, the distal end of the elongated housing comprises a needle assembly having a sheath enshrouding at least a distal portion of a needle in fluid communication with said formulation chamber, wherein the sheath is at least proximally slidable with respect to the needle so as to unsheath the needle during insertion of the needle into a subject, resulting in proximal sliding of the sleeve and proximal movement of the restrainer to the actuated position.

12. The injection device of claim 11, wherein the retention arm or toggle in the actuated position is adapted to prevent the sleeve and sheath from proximal movement once the sleeve and sheath have returned to a needle-enshrouding position.
13. An injection device according to any one of claims 1 to 12 wherein:
the elongated housing comprises a sleeve which is at least adapted to slide proximally between the elongated housing and the formulation chamber and is adapted to engage the restrainer such that proximal movement of the sleeve causes proximal movement of the restrainer;
the distal end of said elongated housing is connected to or is adapted to be connected to a needle assembly comprising a sheath, wherein said sheath is at least proximally slidable with respect to the needle so as to unsheath the needle during insertion of said needle into a subject and so as to slide said sleeve proximally, which results in proximal movement of said restrainer from the first unactuated position to the second actuated position;
the plunger is held in position against said stress by a toggle with distal and proximal ends and connected to the plunger by a pivot point located between said distal and proximal ends and wherein said first surface is in the form of an outwardly directed ledge positioned between the pivot point and the proximal end and adapted to engage said opposed complementary second surface provided in the form of a complementary inwardly directed ledge on or connected to the actuation housing, the proximal end of the toggle comprising a surface adapted to engage a complementary surface of the restrainer when in the unactuated position.
14. The injection device of any one of claims 11 to 13, wherein the sheath is an integral part of the sleeve.
15. The injection device of claim 13 or claim 14, wherein the toggle is biased towards the actuated position to ensure it completes its travel.
16. The injection device of any one of claims 11 to 15, wherein the sleeve and sheath are held in a needle enshrouding position by at least one sleeve spring stressed against a proximal surface of the sleeve which is adapted to engage said second spring.
17. The injection device of any one of claims 11 to 15, wherein a spring is stressed between a distal portion of the sheath and the needle assembly, to ensure the sheath covers the needle tip.
18. The injection device of any one of claims 11 to 17, comprising a one-way valve, optionally a duck bill valve, in the fluid path between the formulation chamber and the distal end of said needle assembly.

19. The injection device of any one of claims 11 to 18, wherein the sheath comprises a distal anatomy contacting surface which assists in positioning the injection device and holding it in position.
20. The injection device of claim 19, wherein the anatomy-contacting surface comprises one or more of soft, spongy or rubberized materials, tacky surface, rough surface, protrusions, ridges or spikes or other textural elements.
21. The injection device of claim 19 or claim 20 which is adapted for intravitreal or suprachoroidal injection, wherein said sheath has a distal, eye-contacting surface.
22. The injection device of any one of claims 19 to 21, wherein said eye-contacting surface has an outer perimeter that defines a circle or modified circle, said eye-contacting surface being annular or in the form of a perforated concave disc, discoid or 3-dimensional annulus surface, with the needle defining the centre of said circle, and wherein the diameter of said circle is between 4 to 10 mm, optionally between 6mm and 8mm.
23. The injection device of any one of claims 1 to 22, wherein said actuation mechanism housing and the elongated housing are detachable from one another to allow placement, removal or replacement of formulation chamber(s) into or from said elongated housing.
24. The injection device of any one of claims 1 to 22, wherein said actuation mechanism housing and the elongated housing are detachable from one another to allow replacement of the elongated housing and formulation chamber after injection with a new elongated housing pre-assembled with fresh formulation chamber.
25. The injection device of any one of claims 1 to 24, wherein the distal end of the elongated housing comprises a needle assembly as an integral part.
26. The injection device of any one of claims 1 to 24, wherein the distal end of the elongated housing is adapted to have a needle assembly removably attached thereto, either through direct attachment to the formulation chamber, or attachment to the elongated housing in a manner which brings the needle assembly into fluid communication with the formulation chamber.
27. The injection device of claim 26, wherein connection of the actuation housing to the elongated housing results in engagement of the plunger with the formulation chamber stopper and resultant positive pressure within said formulation chamber, its stopper, the actuation mechanism or any combination thereof.

28. The injection device of claim 27, wherein when a needle assembly is placed in fluid communication with the distal end of said formulation chamber, said positive pressure results in a small amount of fluid being expelled from the formulation chamber through said needle, the needle being thereby primed with formulation.
29. The injection device of claim 26, wherein the needle assembly comprises a spring at its proximal end and adapted to push proximally against the distal end of the formulation chamber such that attachment of the needle assembly to the elongated housing results in engagement of the plunger with the stopper and positive pressure between said plunger and said needle assembly resulting in a small amount of fluid being expelled from the formulation chamber through said needle, the needle being thereby primed with formulation.
30. The injection device of claim 29, wherein the amount of fluid expelled from the formulation chamber is capable of being adjusted.
31. The injection device of any one of claims 1 to 26, wherein the position of the plunger is adjustable to result in engagement of the plunger with the stopper and positive pressure between the plunger and a needle attached to the elongated housing resulting in a small amount of fluid being expelled from the formulation chamber through said needle, the needle being thereby primed with formulation.
32. The injection device of any one of claims 28 to 31, wherein the needle is part of a needle assembly further comprising a needle cap having a reservoir to receive excess formulation expelled during priming of the needle.
33. The injection device of any one of claims 1 to 32, wherein a dosing mechanism is adjustably coupled to the plunger at the proximal end of the actuation housing, such that a distance between the dosing mechanism and the actuation housing, and therefore an allowable travel distance of the plunger, can be set to a specified value, so that a selected volume of formulation may be operatively dispensed.
34. The injection device of claim 33, wherein the plunger has a proximal end that extends proximally beyond the actuation housing and engages with a cap or knob such that a distance between the cap or knob and the actuation housing may be adjusted, and therefore an allowable travel distance of said plunger is controlled, so that operatively adjustment of the cap allows delivery of a selected volume of formulation.

35. The injection device of claim 33 or claim 34, wherein the dosing mechanism comprises a first internal knob, a second, external dose setting knob, and a dose delivery housing adapted to sit on the proximal end of the actuation housing, wherein the proximal end of the plunger engages with the first knob via a thread with axial:longitudinal pitch X, the first knob engages with the second knob axially, but not longitudinally, and the second external dose setting knob engages with the dose delivery housing via a thread with axial:longitudinal pitch Y, wherein pitch Y is greater than pitch X, such that axial rotation of the second external dose setting knob results in the same degree of axial rotation as the first knob, but greater longitudinal travel of the second external dose setting knob compared to the first knob.

36. The injection device of any one of claims 33 to 35 wherein the coupling of the dosing mechanism to the plunger is configured in a manner which ensures the dosing mechanism is set to a '0' setting when assembled and ready for injection.

37. The injection device of any one of claims 1 to 36, wherein the at least one driving spring is positioned between the plunger and the proximal end of the actuation mechanism housing.

38. The injection device of claim 37, wherein the at least one driving spring comprises a torsion spring that is stressed between the actuation housing and a torsion nut which engages the plunger with a thread, the pitch of said thread defining the mechanical advantage in relation to transmission of force from the spring to the plunger.

39. The injection device of any one of claims 1 to 36, wherein the at least one driving spring is offset compared to the plunger and biases the plunger indirectly.

40. The injection device of claim 39 wherein the offset spring biases the plunger through a lever or geared mechanism providing a mechanical advantage in relation to transmission of force from the spring to the plunger.

41. The injection device of any one of claims 1 to 40 which comprises a mechanism that signals one or more of actuation of the device, completion of the injection, confirmation of dose setting, or lock out of the device after injection.

42. The injection device of claim 41, wherein the signal is auditory, haptic, visual, or electronic optionally configured to interface with one or more devices or applications.

43. The device of claim 42, wherein the signal is visual and effected through movement of the retaining arm or toggle, or movement of the plunger, from an unactuated to an actuated position.

44. The device of any one of claims 1 to 43 which is adapted for single use.
45. The device of claim 44 which comprises the elongated housing with a needle assembly as an integral part thereof.
46. The device of claim 44 or claim 45, wherein the actuation housing and elongated housing, once connected are not adapted to be separated.
47. The device of any one of claims 44 to 46, wherein the actuation mechanism, formulation chamber and elongated housing are provided as separate items for assembly before use.
48. The device of any one of claims 44 to 46, wherein the formulation chamber is an integral part of the elongation housing, being connected to the outer wall of the elongated housing by axially extending ribs with a sleeve adapted to engage the restrainer being slidably positioned between the chamber and the outer wall of the elongated housing.
49. The device of any one of claims 1 to 43 which is adapted for use on multiple patients, for multiple injections, or for injection of different formulations.
50. The device of claim 49 which comprises a restrainer and retainer arm/toggle configuration which allows re-setting of the restrainer and retainer arm/toggle to the unactuated position.
51. The device of claim 49 or claim 50, which comprises a dosing mechanism that is configured to be re-set to a '0' setting after each injection.
52. The device of any one of claims 49 to 51, wherein the distal end of the elongated housing is adapted to have a needle assembly removably attached thereto, either through direct attachment to the formulation chamber, or attachment to the elongated housing in a manner which brings the needle assembly into fluid communication with the formulation chamber, such that separate needle hubs can be used for different patients whilst injecting doses from the same formulation chamber to the different patients.
53. The device of any one of claims 49 to 52, wherein the actuation housing and the elongated housing are adapted to be detachably connected to allow insertion or replacement of the formulation chamber, or replacement of the elongated housing with pre-assembled elongated housing with fresh formulation chamber.

54. An injection device comprising an elongated housing having a proximal end and a distal end, the proximal end comprising an actuation mechanism, wherein:

said elongated housing defines an inner lumen between said proximal and distal ends which includes or is adapted to receive and hold a formulation chamber relative to said actuation mechanism, said formulation chamber also having corresponding proximal and distal ends, and having a stopper between its proximal and distal ends for retaining formulation in said formulation chamber;

said actuation mechanism having corresponding proximal and distal ends, and comprises an actuation housing with a proximal end, and a distal end adapted for engaging said elongated housing, wherein said actuation mechanism includes a plunger, the distal end of said plunger engaging said stopper or being adapted to engage said stopper, and said plunger being in communication with at least one driving spring which biases the plunger distally when the actuation mechanism is primed for injection, wherein said plunger is held in position against said bias by a toggle which has distal and proximal ends, and is connected to the plunger by a pivot point located between said distal and proximal ends, the toggle having an outwardly directed ledge positioned between the pivot point and the proximal end and adapted to engage an opposed inwardly directed ledge on or connected to the actuation housing to hold the plunger in a first unactuated position when the actuation mechanism is primed for injection, the proximal end of the toggle including a surface adapted to engage a complementary surface of a restrainer to hold the toggle in an unactuated position and thereby keep the outwardly directed ledge and opposed inwardly directed ledge in an engaged position, wherein the restrainer translates from an unactuated position or configuration to an actuated position or configuration when triggered, thereby allowing the toggle to deflect to an actuated position thereby uncoupling of the engagement between the outwardly directed ledge and opposed inwardly directed ledge and release of the plunger to move distally;

the elongated housing comprises a sleeve which is at least adapted to slide proximally between the elongated housing and the formulation chamber and is adapted to engage the restrainer such that proximal movement of the sleeve causes proximal movement of the restrainer; and

the distal end of the elongated housing is connected to or is adapted to be connected to a needle assembly comprising a sheath, said sheath being either an integral part of said sleeve or being adapted to engage the distal end of said sleeve, wherein the sheath is at least proximally slidable with respect to the needle so as to unsheath the needle during insertion of said needle into a subject and so as to slide the sleeve proximally, which results in proximal movement of said restrainer from the unactuated position to the actuated position, uncoupling of the engagement

between the outwardly directed ledge and opposed inwardly directed ledge, and release of the plunger to move distally.

55. The injection device of claim 54, wherein the triggering force required to allow uncoupling of the engagement between the first and second surfaces and release of the plunger to move distally is inversely proportional to a value a/b , wherein a is the distance between the proximal end of the toggle and the pivot point and b is the distance between the first surface and the pivot point, allowing regulation of the triggering force by regulation of the value a/b .

56. The injection device of claim 55 for use in an injection indicating low triggering force and configured such that b is substantially smaller than a .

57. The injection device of claim 56 wherein the value of a divided by b is greater than or equal to 1.

58. The injection device of any one of claims 54 to 57, wherein the toggle is biased towards the actuated position to ensure it completes its travel.

59. The injection device of any one of claims 54 to 58, wherein the retention arm or toggle in the second actuated position, is adapted to prevent the sleeve and sheath from proximal movement once the sleeve and sheath have returned to a needle-enshrouding position.

60. The injection device of claim 59, wherein the sleeve and sheath are held in a needle enshrouding position by at least one sleeve spring stressed against a proximal surface of the sleeve which is adapted to engage said second spring.

61. The injection device of claim 59, wherein a biasing means is provided, stressed between a distal portion of the sheath and the needle assembly, to ensure the sheath covers the needle tip.

62. The injection device of any one of claims 54 to 61, comprising a one-way valve, optionally a duck bill valve, in the fluid path between the formulation chamber and the distal end of said needle assembly.

63. The injection device of any one of claims 54 to 62, wherein the sheath comprises a distal anatomy contacting surface which assists in positioning the injection device and holding it in position.

64. The injection device of claim 63, wherein the anatomy-contacting surface comprises one or more of soft, spongy or rubberized materials, tacky surface, rough surface, protrusions, ridges or spikes or other textural elements.
65. The injection device of claim 63 or claim 64 which is adapted for intravitreal or suprachoroidal injection, wherein said sheath has a distal, eye-contacting surface.
66. The injection device of any one of claims 63 to 65, wherein said eye-contacting surface has an outer perimeter that defines a circle or modified circle, said eye-contacting surface being annular or in the form of a perforated concave disc, discoid or 3-dimensional annulus surface, with the needle defining the centre of said circle, and wherein the diameter of said circle is between 4 to 10 mm, optionally between 6mm and 8mm.
67. The injection device of any one of claims 54 to 66, wherein said actuation mechanism housing and the elongated housing are detachable from one another to allow placement, removal or replacement of formulation chamber(s) into or from said elongated housing.
68. The injection device of any one of claims 54 to 67, wherein said actuation mechanism housing and the elongated housing are detachable from one another to allow replacement of the elongated housing and formulation chamber after injection with a new elongated housing pre-assembled with fresh formulation chamber.
69. The injection device of any one of claims 54 to 68, wherein the distal end of the elongated housing comprises a needle assembly as an integral part.
70. The injection device of any one of claims 54 to 68, wherein the distal end of the elongated housing is adapted to have a needle assembly removably attached thereto, either through direct attachment to the formulation chamber, or attachment to the elongated housing in a manner which brings the needle assembly into fluid communication with the formulation chamber.
71. The injection device of claim 70, wherein connection of the actuation housing to the elongated housing results in engagement of the plunger with the formulation chamber stopper and concomitant positive pressure within said formulation chamber, its stopper, the actuation mechanism or any combination thereof.
72. The injection device of claim 71, wherein when a needle assembly is placed in fluid communication with the distal end of said formulation chamber, said positive pressure results in a

small amount of fluid being expelled from the formulation chamber through said needle, the needle being thereby primed with formulation.

73. The injection device of claim 70, wherein the needle assembly comprises a spring at its proximal end and adapted to push proximally against the distal end of the formulation chamber such that attachment of the needle assembly to the elongated housing results in engagement of the plunger with the stopper and positive pressure between said plunger and said needle assembly resulting in a small amount of fluid being expelled from the formulation chamber through said needle, the needle being thereby primed with formulation.

74. The injection device of any one of claims 54 to 70, wherein the position of the plunger is adjustable to result in engagement of the plunger with the stopper and positive pressure between the plunger and a needle attached to the elongated housing resulting in a small amount of fluid being expelled from the formulation chamber through said needle, the needle being thereby primed with formulation.

75. The injection device of any one of claims 72 to 74, wherein the needle is part of a needle assembly comprising a needle cap having a reservoir to receive excess formulation expelled during priming of the needle.

76. The injection device of any one of claims 54 to 75, wherein a dosing mechanism is adjustably coupled to the plunger at the proximal end of the actuation housing, such that a distance between the dosing mechanism and the actuation housing, and therefore an allowable travel distance of the plunger, can be set to a specified value, so that a selected volume of formulation may be operatively dispensed.

77. The injection device of claim 76, wherein the plunger has a proximal end that extends proximally beyond the actuation housing and engages with a cap or knob such that a distance between the cap and the actuation housing may be adjusted, and therefore an allowable travel distance of said plunger is controlled, so that operatively adjustment of the cap allows delivery of a selected volume of formulation.

78. The injection device of claim 77, wherein adjustment of the cap or knob before actuation sets the device for delivery of a selected volume of formulation on actuation of the device.

79. The injection device of claim 78, wherein the selected volume is capable of being adjusted in discrete increments.

80. The injection device of claim 76 or claim 77, wherein the dosing mechanism comprises a first internal knob, a second, external dose setting knob, and a dose delivery housing adapted to sit on the proximal end of the actuation housing, wherein the proximal end of the plunger engages with the first knob via a thread with axial:longitudinal pitch X, the first knob engages with the second knob axially, but not longitudinally, and the second external dose setting knob engages with the dose delivery housing via a thread with axial:longitudinal pitch Y, wherein pitch Y is greater than pitch X, such that axial rotation of the second external dose setting knob results in the same degree of axial rotation as the first knob, but greater longitudinal travel of the second external dose setting knob compared to the first knob.

81. The injection device of any one of claims 76 to 80 wherein the coupling of the dosing mechanism to the plunger is configured in a manner which ensures the dosing mechanism is set to a '0' setting when assembled and ready for injection.

82. The injection device of any one of claims 54 to 81, wherein the at least one driving spring is positioned between the plunger and the proximal end of the actuation mechanism housing.

83. The injection device of claim 82, wherein the at least one driving spring comprises a torsion spring that is stressed between the actuation housing and a torsion nut which engages the plunger with a thread, the pitch of said thread defining the mechanical advantage in relation to transmission of force from the spring to the plunger.

84. The injection device of any one of claims 54 to 81, wherein the at least one driving spring is offset compared to the plunger and biases the plunger indirectly.

85. The injection device of claim 84 wherein the offset spring biases the plunger through a lever or geared mechanism providing a mechanical advantage in relation to transmission of force from the spring to the plunger.

86. The injection device of any one of claims 54 to 85 which comprises a mechanism that signals one or more of actuation of the device, completion of the injection, confirmation of dose setting, or lock out of the device after injection.

87. The injection device of claim 86, wherein the signal is auditory, haptic, visual, or electronic optionally configured to interface with one or more devices or applications.

88. The device of claim 87, wherein the signal is visual and effected through movement of the retaining arm or toggle, or movement of the plunger, from an unactuated to an actuated position.

89. The device of any one of claims 54 to 88 which is adapted for single use.
90. The device of claim 89 which comprises the elongated housing with a needle assembly as an integral part thereof.
91. The device of claim 89 or claim 90, wherein the actuation housing and elongated housing, once connected are not adapted to be separated.
92. The device of any one of claims 89 to 91, wherein the actuation mechanism, formulation chamber and elongated housing are provided as separate items for assembly before use.
93. The device of any one of claims 89 to 92, wherein the formulation chamber is an integral part of the elongation housing, being connected to the outer wall of the elongated housing by axially extending ribs with a sleeve adapted to engage the restrainer being slidably positioned between the chamber and the outer wall of the elongated housing.
94. The device of any one of claims 54 to 88 which is adapted for use on multiple patients, for multiple injections, or for injection of different formulations.
95. The device of claim 94 which comprises a restrainer and retainer arm/toggle configuration which allows re-setting of the restrainer and retainer arm/toggle to the unactuated position.
96. The device of claim 94 or claim 95, which comprises a dosing mechanism that is configured to be re-set to a '0' setting after each injection.
97. The device of any one of claims 94 to 96, wherein the distal end of the elongated housing is adapted to have a needle assembly removably attached thereto, either through direct attachment to the formulation chamber, or attachment to the elongated housing in a manner which brings the needle assembly into fluid communication with the formulation chamber, such that separate needle hubs can be used for different patients whilst injecting doses from the same formulation chamber to the different patients.
98. The device of any one of claims 94 to 97, wherein the actuation housing and the elongated housing are adapted to be detachably connected to allow insertion or replacement of the formulation chamber, or replacement of the elongated housing with pre-assembled elongated housing with fresh formulation chamber.

99. The device of any one of claims 1 to 98, wherein the distal end of the elongated housing is connected to or is adapted to be connected to a needle assembly comprising at least a distally extending needle at its distal end which is enshrouded by a cap when not in use, said cap being adapted to fully enshroud at least the distally extending needle, optionally also including means to ensure that said cap does not rotate axially with respect to said main body when connecting the needle assembly to said injection device.

100. The device of claim 99, wherein the cap comprises a seal in which the distally extending needle is inserted.

101. The device of claim 100, wherein the cap comprises a tip section slidably retained at least partially inside a proximal body that connects to the elongated housing or needle assembly, wherein the tip section may slide distally within or at least partially beyond the proximal body, wherein the seal is located in the tip section and wherein before priming of the needle the needle is inserted in the seal and the tip section is not fully extended distally in relation to the proximal body.

102. The device of claim 101, wherein when the needle is primed, the pressure from the priming fluid pushes the seal and the tip section distally.

103. A needle hub adapted to be attached to an injection device according to any one of claims 1 to 44, 46 to 89 or 91 to 102 comprising a needle and a body with the injection end of the needle protruding distally from it, the proximal end of the needle hub being adapted to connect to the engagement so that the needle can operatively communicate with the formulation chamber, the needle hub also including a sheath enshrouding the distal needle and main body, the proximal end of the sheath being operatively adapted, once the hub is connected to the injection device, to: retain the main body of the needle assembly within the sheath; to engage a sleeve of said injection device; and to fit and slide relative to the injection device.

104. The needle hub of claim 103 also comprising a proximal end having a proximal end of the needle protruding proximally from it.

105. The needle hub of claim 103 or claim 104, comprising a one-way valve, optionally a duck bill valve, in the fluid path within the body of said needle assembly.

106. A needle hub for attachment to an injection device according to any one of claims 1 to 44, 46 to 89 or 95 to 102 comprising a main body having a proximal body and a distal body, the main body being either connected to a member adapted to engage the distal end of the elongated

housing or formulation chamber or having a proximal end adapted to engage the distal end of the elongated housing or formulation chamber, the proximal body having a proximal needle extending proximally from it, the distal body comprising a distal needle extending distally from it, the proximal and distal bodies being adapted to connect together with a filter enclosed between them and between the two needles, the needle hub also comprising a sheath enshrouding the needle and main body, the proximal end of the sheath being adapted to: retain the main body of a needle assembly within the sheath when not in use; to engage the sleeve of said injection device; and to fit and slide within the elongated housing.

107. The needle hub of claim 106, wherein the proximal needle has a larger gauge than the distal needle.

108. The needle hub of claim 107, wherein the distal needle has a gauge of 25 (approximately 0.5mm outer diameter) or finer, preferably gauge 27 (approximately 0.4mm outer diameter) or finer.

109. The needle hub of any one of claims 106 to 108, comprising a one-way valve, optionally a duck bill valve, between the proximal needle and the distal needle within the body of said needle assembly.

110. The needle hub of any one of claims 106 to 109, wherein the sheath comprises a distal anatomy contacting surface which assists in positioning the injection device and holding it in position.

111. The needle hub of claim 110, wherein the anatomy-contacting surface comprises one or more of soft, spongy or rubberized materials, tacky surface, rough surface, protrusions, ridges or spikes or other textural elements.

112. The needle hub of claim 110 or claim 111 which is adapted for intravitreal or suprachoroidal injection, wherein said sheath has a distal, eye-contacting surface.

113. The needle hub of any one of claims 103 to 112, wherein said eye-contacting surface has an outer perimeter that defines a circle or modified circle, said surface being annular or in the form of a perforated concave disc, discoid or 3-dimensional annulus surface, with the needle defining the centre of said circle, and wherein the diameter of said circle is between 4 to 10 mm, optionally between 6mm and 8mm.

114. The needle hub of any one of claims 103 to 113 comprising a cap when not in use, said cap being adapted to fully enshroud at least the distal end of said needle hub, optionally also including means to ensure that said cap does not rotate axially with respect to said main body when connecting the needle hub to said injection device.

115. The needle hub of claim 114, wherein the cap has a reservoir to receive excess formulation expelled during priming of the needle.

116. The needle hub of claim 114 or 115 wherein the cap is configured to be removably attachable to the distal end of the needle hub, such that it is removed when the needle hub is in an operable state and attached when the needle hub is not prepared for operation.

117. The needle hub of claim 114 or 115 wherein the cap is configured to attach the needle hub to the elongated housing or formulation chamber.

118. A needle hub adapted to be attached to an injection device, the injection device including a formulation chamber and an engagement allowing connection to a formulation chamber, the needle hub comprising a needle and a body with the injection end of the needle protruding distally from it, the proximal end of the needle hub being adapted to connect to the engagement so that the needle can operatively communicate with the formulation chamber, the needle hub also including a sheath enshrouding the distal needle and main body, the proximal end of the sheath being operatively adapted, once the hub is connected to the injection device, to: retain the main body of the needle assembly within the sheath; to engage a sleeve of said injection device; and to fit and slide relative to the injection device, said needle hub optionally also comprising a cap which fully enshrouds at least the distal end of said needle hub.

119. The needle hub of claim 118 wherein a proximal end of the needle protrudes proximally from the proximal end.

120. The needle hub of any one of claims 114 to 119, wherein the cap comprises a seal in which the distally extending needle is inserted.

121. The needle hub of claim 120, wherein the cap comprises a tip section slidably retained at least partially inside a proximal body that connects to the elongated housing or needle assembly, wherein the tip section may slide distally within or at least partially beyond the proximal body, wherein the seal is located in the tip section and wherein before priming of the needle the needle is inserted in the seal and the tip section is not fully extended distally in relation to the proximal body.

122. The needle hub of claim 121, wherein when the needle is primed, the pressure from the priming fluid pushes the seal and the tip section distally.

123. An actuator mechanism for an injection device, the mechanism having a plunger, the distal end of the plunger being adapted to engaging a stopper, and the plunger being in communication with at least one driving spring which biases the plunger distally when the actuation mechanism is primed for injection,

wherein the plunger is held in position against said bias by a retention arm or toggle having at least one first surface adapted to engage an opposed complementary second surface to hold said plunger in an unactuated position when the actuation mechanism is primed for injection, the first and second surfaces being held in an engaged position by a restrainer which translates from an unactuated position or configuration to an actuated position or configuration when triggered, thereby allowing uncoupling of the engagement between the first and second surfaces and release of the plunger to move distally.

124. The actuator mechanism of claim 123, comprising a retention toggle which has distal and proximal ends, and is connected to the plunger by a pivot point located between said distal and proximal ends.

125. The actuator mechanism of claim 124, wherein said first surface of the toggle is in the form of an outwardly directed ledge positioned between the pivot point and the proximal end and adapted to engage an opposed complementary second surface in the form of an inwardly directed ledge on or connected to the actuation housing, the proximal end of the toggle including a surface adapted to engage a complementary surface of the restrainer.

126. The actuator mechanism of claim 124 or claim 125, wherein the triggering force required to allow uncoupling of the engagement between the first and second surfaces and release of the plunger to move distally is inversely proportional to a value a/b , wherein a is the distance between the proximal end of the toggle and the pivot point and b is the distance between the first surface and the pivot point, allowing regulation of the triggering force by regulation of the value a/b .

127. The actuator mechanism of claim 126 for use in an injection indicating low triggering force and configured such that b is substantially smaller than a .

128. The injection device of claim 126 wherein the value of a divided by b is greater than or equal to 1.

129. The actuator mechanism of any one of claims 123 to 128, wherein the arm or toggle is biased towards the actuated position to ensure it completes its travel.
130. The actuator mechanism of any one of claims 123 to 129, wherein the retention arm or toggle in the actuated position and the actuator mechanism housing are adapted to prevent proximal movement of the plunger.
131. The actuator mechanism of any one of claims 123 to 130, wherein a dosing mechanism is adjustably coupled to the plunger at the proximal end of the actuator mechanism housing, such that a distance between the dosing mechanism and the actuator mechanism housing, and therefore an allowable travel distance of the plunger, can be set to a specified value, so that a selected volume of formulation may be operatively dispensed.
132. The actuator mechanism of claim 131, wherein the plunger has a proximal end that extends proximally beyond the actuator mechanism housing and engages with a cap such that a distance between the cap and the actuation housing may be adjusted, and therefore an allowable travel distance of said plunger is controlled, so that operatively adjustment of the cap allows delivery of a selected volume of formulation.
133. The actuator mechanism of claim 131 or 132, wherein the dosing mechanism comprises a first internal knob, a second, external dose setting knob, and a dose delivery housing adapted to sit on the proximal end of the actuation housing, wherein the proximal end of the plunger engages with the first knob via a thread with axial:longitudinal pitch X, the first knob engages with the second knob axially, but not longitudinally, and the second external dose setting knob engages with the dose delivery housing via a thread with axial:longitudinal pitch Y, wherein pitch Y is greater than pitch X, such that axial rotation of the second external dose setting knob results in the same degree of axial rotation as the first knob, but greater longitudinal travel of the second external dose setting knob compared to the first knob.
134. The actuator mechanism device of any one of claims 131 to 133, wherein the coupling of the dosing mechanism to the plunger is configured in a manner which ensures the dosing mechanism is set to a '0' setting when assembled and ready for injection.
135. The actuator mechanism of any one of claims 123 to 134, wherein the at least one driving spring is positioned between the plunger and the proximal end of the actuation mechanism housing.

136. The actuator mechanism of claim 135, wherein the at least one driving spring comprises a torsion spring that is stressed between the actuation housing and a torsion nut which engages the plunger with a thread, the pitch of said thread defining the mechanical advantage in relation to transmission of force from the spring to the plunger.
137. The actuator mechanism of any one of claims 123 to 134, wherein the driving spring is offset compared to the plunger and biases the plunger indirectly.
138. The actuator mechanism of claim 137 wherein the offset spring biases the plunger through a lever or geared mechanism providing a mechanical advantage in relation to transmission of force from the spring to the plunger.
139. The actuator mechanism of any one of claims 123 to 138 which comprises a mechanism that signals one or more of actuation of the device, completion of the injection, confirmation of dose setting, or lock out of the device after injection.
140. The actuator mechanism of claim 139, wherein the signal is auditory, haptic, visual, or electronic optionally configured to interface with one or more devices or applications.
141. The actuator mechanism of claim 140, wherein the signal is visual and effected through movement of the retaining arm or toggle, or movement of the plunger, from an unactuated to an actuated position.
142. The actuator mechanism of any one of claims 123 to 141, which comprises a restrainer and retainer arm/toggle configuration which allows re-setting of the restrainer and retainer arm/toggle to the unactuated position.
143. The actuator mechanism of claim 142, which comprises a retention toggle that is configured to interact with complementary features on the inner wall of the actuation housing such that the toggle returns to its unactuated position when the plunger is moved proximally against the bias of the driving spring.
144. The actuator mechanism of claim 143, wherein the toggle and the restrainer are configured to allow the toggle to return to its unactuated position and to again hold and re-restrain the toggle such that the first and second surfaces are again in an engaged position.

145. The actuator mechanism of claim 143 or claim 144 wherein the interacting surfaces of the toggle, restrainer and actuation housing are configured to allow re-setting of the restrainer and toggle to the unactuated position.

146. An elongated housing assembly for use with an injection device according to any one of claims 1 to 102 comprising proximal and distal ends and which defines an inner lumen between said proximal and distal ends which includes or is adapted to receive and hold a formulation chamber relative to said actuation mechanism, said formulation chamber also having corresponding proximal and distal ends, and having a stopper between its proximal and distal ends for retaining formulation in said formulation chamber, and wherein said elongated housing also comprises a sleeve which is at least proximally slidable between the elongated housing and the formulation chamber and is adapted to engage the restrainer of the actuation housing, and wherein insertion of a needle connected to the elongated housing into a subject results in the sleeve sliding proximally.

147. The elongated housing of claim 146, wherein operatively, the distal end of the elongated housing comprises a needle assembly having a sheath enshrouding at least a distal portion of a needle in fluid communication with said formulation chamber, said sheath being either an integral part of said sleeve or being adapted to engage the distal end of said sleeve, and wherein the sheath is at least proximally slidable with respect to the needle so as to unsheath the needle during insertion of the needle into a subject, resulting in proximal sliding of the sleeve.

148. The elongated housing of claim 147, wherein the distal end of said elongated housing is connected to or is adapted to be connected to the needle assembly.

149. The elongated housing of any one of claims 146 to 148 which is adapted for single use.

150. The elongated housing of claim 149 which comprises the elongated housing with a needle assembly as an integral part thereof.

151. The elongated housing of claim 149 or claim 150, wherein the elongated housing and actuation housing, once connected are not adapted to be separated.

152. The elongated housing of any one of claims 146 to 151, wherein the formulation chamber is formed as an integral part of the elongated housing, being connected to the wall of the elongated housing by axially inwardly extending ribs with the sleeve being slidably positioned between the chamber and the wall of the elongated housing.

153. The elongated housing of any one of claims 146 to 152 which is adapted for use on multiple patients, for multiple injections, or for injection of different formulations.

154. The elongated housing of claim 153, wherein the distal end of the elongated housing is adapted to have a needle assembly removably attached thereto, either through direct attachment to the formulation chamber, or attachment to the elongated housing in a manner which brings the needle assembly into fluid communication with the formulation chamber, such that separate needle hubs can be used for different patients whilst injecting doses from the same formulation chamber to the different patients.

155. The elongated housing of claim 153 or claim 154, wherein the elongated housing is adapted to be detachably connected to the actuation housing to allow insertion or replacement of the formulation chamber, or replacement of the elongated housing with pre-assembled elongated housing with fresh formulation chamber.

156. The elongated housing of any one of claims 146 to 155, wherein the distal end of the elongated housing is connected to or is adapted to be connected to a needle assembly comprising at least a distally extending needle at its distal end which is enshrouded by a cap when not in use, said cap being adapted to fully enshroud at least the distally extending needle, optionally also including means to ensure that said cap does not rotate axially with respect to said main body when connecting the needle hub to said injection device.

157. The elongated housing of claim 156, wherein the cap comprises a seal in which the distally extending needle is inserted.

158. The elongated housing of claim 157, wherein the cap comprises a tip section slidably retained at least partially inside a proximal body that connects to the elongated housing or needle assembly, wherein the tip section may slide distally within or at least partially beyond the proximal body, wherein the seal is located in the tip section and wherein before priming of the needle the needle is inserted in the seal and the tip section is not fully extended distally in relation to the proximal body.

159. The elongated housing of claim 158, wherein when the needle is primed, the pressure from the priming fluid pushes the seal and the tip section distally.

160. A dose delivery mechanism for an injection device, the injection device comprising a body with a distal end which, operatively, has a needle assembly attached thereto and a proximal end

comprising an actuation mechanism with a plunger with distal and proximal ends, the injection device further including a formulation chamber also with distal and proximal ends and including a stopper between its distal and proximal ends and formulation between the stopper and the distal end of the formulation chamber, wherein the distal end of the plunger is adapted to engage the stopper, and wherein said dose delivery mechanism is adjustably coupled to the proximal end of the plunger such that a distance between the dosing mechanism and the device body, and therefore an allowable travel distance of the plunger, can be set to a specified value to set a selected volume of formulation for delivery.

161. The dose delivery mechanism of claim 160, wherein the plunger has a proximal end that extends proximally beyond the device body and engages adjustably with a knob or cap such that the distance between the knob or cap and the device body may be adjusted, whereby the allowable travel distance of the plunger is controlled, so that operatively adjustment of the knob or cap allows setting of a selected volume of formulation for delivery.

162. The dose delivery mechanism of claim 160 or claim 161, wherein the coupling of the dosing mechanism to the plunger is configured in a manner which ensures the dosing mechanism is set to an initial value setting when assembled and ready for injection.

163. The dose delivery mechanism of any one of claims 160 to 162, which comprises a first internal knob, a second, external dose setting knob, and a dose delivery housing adapted to sit on the proximal end of the device body, wherein the proximal end of the plunger engages with the first knob via a first thread with axial:longitudinal pitch X, the first knob engages with the second knob axially, but not longitudinally, and the second external dose setting knob engages with the dose delivery housing via a second thread with axial:longitudinal pitch Y, wherein pitch Y is greater than pitch X, such that axial rotation of the second external dose setting knob results in the same degree of axial rotation as the first knob, but greater longitudinal travel of the second external dose setting knob compared to the first knob.

164. The dose delivery mechanism of claim 163, wherein operatively the longitudinal position of the plunger is adjusted by the first knob until substantially no play exists between the first knob and the body of the injector device, and between the actuation mechanism and the plunger.

165. The dose delivery mechanism of claim 164, wherein operatively the second knob is assembled into the dose delivery housing via the second thread and adjusted such that it shows an initial value in a window of the dose delivery housing, and the assembled second knob and dose

delivery housing are then fitted over the first knob such that the initial value stays in a window of the dose delivery housing and the first and second knobs are axially engaged, whereby the dose delivery mechanism is placed in an initial state corresponding to the initial value and ready for dose setting by adjustment of the second knob within the dose delivery housing.

166. The dose delivery mechanism of claim 165, wherein the initial value is zero.

167. The dose delivery mechanism of any one of claims 162 to 166, wherein the assembly of the second knob to the first knob such that the initial value is displayed in the window of the dose delivery housing is independent to its rotational position about a longitudinal axis of the injection device.

168. The dose delivery mechanism of any one of claims 163 to 167, wherein the distal external surface of the first knob has pips or ridges which engage with complementary ridges or pips on the proximal surface of the device body such that axial rotation of the first knob is stepped, and not free; whereby dosages can be set in stepped, discrete amounts, and whereby once the first knob has been adjusted to a desired setting it does not move axially freely.

169. The dose delivery mechanism of any one of claims 163 to 168, wherein the injection device is an injection device according to any one of claims 1 to 102.

170. A method for operating an injection device, the injection device having an elongated housing having a proximal end and a distal end, the proximal end having an actuation mechanism and the distal end having or being adapted to have a needle attached thereto, the injection device further including a formulation chamber including a stopper,

the actuation mechanism including a plunger, the distal end of the plunger being adapted to engage the stopper, the plunger being biased towards the distal end when the actuation mechanism is primed for injection, the plunger being held in position against the bias by a retention arm or toggle, so as to hold the plunger in an unactuated position when the actuation mechanism is primed for injection, the plunger being held in an engaged position by a restrainer which is adapted to translate from an unactuated position or configuration to an actuated position or configuration when triggered,

the method comprising bringing the device into an operative position; triggering the restrainer to release the plunger from the engaged position, the plunger then moving distally to deliver formulation from the formulation chamber.

171. The method of claim 170, wherein the device further includes a needle, and wherein prior to triggering the restrainer, the device is primed so that formulation fills the needle.

172. The method of claim 170 or claim 171, wherein a selectively adjustable proximal cap is provided, the method further including the step, prior to triggering the restrainer, of selecting a desired dose by adjusting the proximal cap.

173. The method of any one of claims 170 to 172, wherein the step of bringing the device into an operative position further comprises positioning the device adjacent to a desired anatomical location on a patient.

174. The method of any one of claims 166 to 168, further comprising the step of aligning and engaging positioning or alignment structures provided distally on the injection device relative to specific features of the anatomy of the patient.

175. The method of any one of claims 170 to 173, wherein the injection device includes a moveable distal projection, and a needle, and the step of triggering the restrainer is initiated by engaging the distal projection with a surface of a patient.

176. The method of any one of claims 170 to 174, wherein the injection device further includes a dose delivered indicator, and wherein the method further includes the step of activating the dose delivered indicator after the restrainer is triggered.

177. The method of claim 170, including the step of re-setting the device for re-use after delivery of formulation.

178. The method of any one of claims 170 to 177, wherein the restrainer and retainer arm/toggle are configured to allow re-setting of the restrainer and retainer arm/toggle to the unactuated position.

179. The method of claim 178, wherein the retainer arm/toggle is a toggle and further comprising moving the plunger proximally against the bias of the driving spring after triggering the injection device to return the toggle to its unactuated position, wherein the toggle is configured to interact with complementary features on the inner wall of the actuation housing to effect its return to its unactuated position and the toggle and the restrainer are configured to allow the toggle to return to its unactuated position and to again hold and re-restrain the toggle such that the first and second surfaces are again in an engaged position.

180. The method of claim 179, wherein the interacting surfaces of the toggle, restrainer and actuation housing are configured to allow returning of the restrainer and toggle to the unactuated position.