



(51) International Patent Classification:

A61M 5/168 (2006.01) *A61M 5/145* (2006.01)
A61M 5/142 (2006.01) *A61M 5/148* (2006.01)

(21) International Application Number:

PCT/GB2017/053859

(22) International Filing Date:

21 December 2017 (21.12.2017)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

1622036.0 22 December 2016 (22.12.2016) GB

(71) Applicant: **CAMBRIDGE MECHATRONICS LIMITED** [GB/GB]; Cambridge Mechatronics Ltd, The Westbrook Centre, Building 6, Cambridge CB4 1YG (GB).

(72) Inventor: **HOWARTH, James**; c/o Cambridge Mechatronics Ltd, The Westbrook Centre, Building 6, Cambridge CB4 1YG (GB).

(74) Agent: **LALLY, Parminder**; Cambridge Mechatronics Ltd, The Westbrook Centre, Building 6, Cambridge CB4 1YG (GB).

(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA,

SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

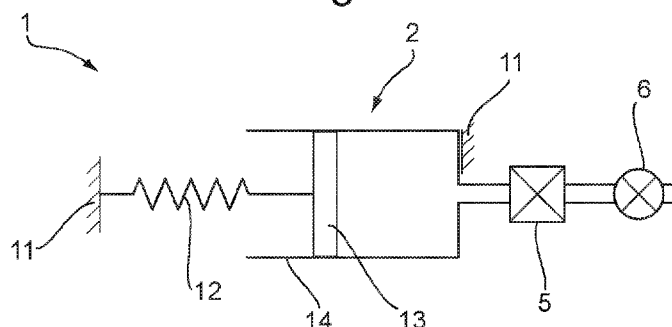
(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(54) Title: THERAPEUTIC PRODUCT DELIVERY DEVICE

Fig. 1



(57) Abstract: A therapeutic product delivery device delivers metered volumes of a therapeutic product. A pressurised reservoir contains the therapeutic product. A variable-sized orifice is in fluid communication with the reservoir for flow of the therapeutic product through the orifice. An shape memory alloy wire is configured to change the size of the orifice to vary the flow rate of the therapeutic product.



Therapeutic Product Delivery Device

The present invention relates to a therapeutic product delivery device for delivering volumes of a therapeutic product.

Therapeutic products such as insulin are often administered to the human body with
5 infusion pumps. Current devices typically deliver the therapeutic product by means of a mechanical force (such as a spring) to pressurise a reservoir containing the therapeutic product and a passive flow restrictor (such as an orifice or microcapillaries) to control the basal rate delivery. The bolus delivery is commonly delivered with the use of mechanical buttons. Current devices are typically limited by their inability to control the flow rate of
10 the therapeutic product through the passive flow restrictor so they must resort to bulky separate delivery mechanisms to deliver the bolus dosage. An electrically driven pump may be used, in conjunction with a toothed gearing mechanism to accurately vary the flow rate. Such a mechanism is necessarily heavy and bulky.

For the example of insulin, the flow range required to cover both basal and bolus
15 insulin delivery for a typical population of patients may be of the order of three orders of magnitude. For example, the flow rate range may be 0.025 to 25 U/hour (U represents an international unit of insulin which is the biological equivalent of 34.7 μg of human insulin), in increments of 0.025 U/hour. Thus the required flow rate range varies by a factor of about a thousand, and the required resolution is about one in a thousand.

20 According to the present invention, there is provided a therapeutic product delivery device for delivering volumes of a therapeutic product, the device comprising: a pressurised reservoir containing the therapeutic product, the therapeutic product being a fluid; a variable-sized orifice in fluid communication with the reservoir for flow of the therapeutic product through the orifice; and an electrically driven actuator configured to
25 change the size of the orifice to vary the flow rate of the therapeutic product.

It has been appreciated that an electrically driven actuator can be used to directly vary the orifice size of a variable-sized orifice that acts as a variable flow restrictor to control the flow rate of the delivered therapeutic product within the required range without using a separate mechanism and without using a gearing mechanism.

30 Advantageously, the actuator may comprise a shape memory alloy (SMA) wire. Although use of an SMA wire actuator is known in insulin delivery devices, in the known devices this is in conjunction with a gearing mechanism to drive delivery of the insulin and therefore complex and bulky. In the device of the invention, an SMA wire actuator directly acts on a variable orifice to vary the orifice size and vary the flow rate, obviating the need

for a gearing mechanism. Given the range and accuracy required, it is surprising that such a direct drive mechanism is suitable. However, it has been appreciated that with appropriate control, an SMA wire actuator can achieve range and accuracy similar to that achieved with a gearing mechanism.

5 SMA wire actuators are compact owing to the small size of the wire, which may be as little as 25 micron diameter for example. An SMA wire when activated contracts up to 4% of its length. Such a wire with a length of for example 10cm is therefore capable of a length contraction of up to 4 mm. It has been appreciated by experiment and analysis that with suitable control, a length accuracy in of the order of 1 micron is achievable, providing
10 the desired one in a thousand accuracy.

Heating of the wire can be readily carried out by passing an electric current through the wire, while cooling between actuations occurs rapidly owing to the small diameter of the wire. Furthermore, the length of the wire can be ascertained by measuring the resistance of the wire using a suitable electrical circuit, allowing accurate closed loop control. These
15 properties provide a variable valve which can be accurately controlled and monitored to ensure accurate delivery doses. Precision can be maintained at both the lowest flow rate, the basal flow, and at the highest rate, the bolus flow. Compared to a toothed geared mechanism, such a controlled SMA actuator mechanism is lighter, less complex and less bulky.

20 The actuator may be configured to change the size of the orifice within a range in which the orifice is always open.

The actuator may be controlled to deliver a flow rate of the therapeutic product that varies between a basal rate of the therapeutic product and an increased bolus rate of the therapeutic product

25 To allow better understanding, an embodiment of the present invention will now be described by way of non-limitative example with reference to the accompanying drawings, in which:

Fig. 1 is a schematic side view of a therapeutic product delivery device in a first form;

30 Fig. 2 is a schematic side view of a therapeutic product delivery device in a second form;

Figs. 3 and 4 are side views of a first valve in two operative states;

Fig. 5 is a cross-sectional view of the first valve in the operative state shown in Fig.

4;

Figs. 6 and 7 are side views of a second valve in two operative states;
Figs. 8 and 9 are side views of a third valve in two operative states;
Fig. 10 is a cross-sectional view of an inner tube of the third valve;
Figs. 11 and 12 are schematic side view of two alternative actuator arrangements;

5 and

Fig. 13 is a diagram of a control system for the therapeutic product delivery device.

The different embodiments described below include common elements which are given common reference numerals. For brevity, the description of the common elements is not repeated but applies equally to all the embodiments.

10 Figs. 1 and 2 show two alternative forms of a therapeutic product delivery device 1. The therapeutic product delivery device 1 is configured to deliver volumes of a therapeutic product that may be metered.

The therapeutic product is a fluid, typically a liquid. The therapeutic product may in general be of any type and have any therapeutic effect. By way of example, the therapeutic
15 product may be insulin.

The therapeutic product may be a product which is desired to be delivered at a flow rate that is normally a basal rate, but on occasion needs to be increased to a bolus rate.

The therapeutic product delivery device 1 is arranged as follows.

In the first form shown in Fig. 1, the therapeutic product delivery device 1
20 comprises a pressurised reservoir 2 in the form of a syringe. The reservoir 2 comprises a cylinder 14 and a plunger 13 which is a piston that slides in the cylinder 14. The reservoir 2 contains the therapeutic product inside the cylinder 14.

A compressive spring 12 is connected to a fixed body 11 and to the plunger 13 and applies a force pushing the plunger 13 into the cylinder 14. The cylinder 14 is also
25 connected to the fixed body 11 so that the spring 12 and the plunger 13 pressurise the therapeutic product within the cylinder 14.

In the second form shown in Fig. 2, the therapeutic product delivery device 1 comprises a pressurised reservoir 2 in the form of a container that comprises a flexible wall 7. The reservoir 2 contains the therapeutic product.

30 A compressive spring 12 is connected to the fixed body 11 and to the flexible wall 7 and applies a force pushing against the flexible wall 7. The flexible wall 7 is also connected to the fixed body 11 so that the spring 12 pressurises the therapeutic product within the reservoir 2.

In each of the first and second forms, the therapeutic product delivery device 1 also

includes a variable valve 5 that is in fluid communication with the reservoir 2. The variable valve 5 controls the flow rate of the therapeutic product out of the reservoir 2. Possible forms of the variable valve 5 are described below.

5 An additional, shut-off valve 6 is arranged in series with the variable valve 5, in this example downstream of the variable valve 5, although it could alternatively be upstream of the variable valve 5. The shut-off valve 6 is configured to close the flow of the therapeutic product from the reservoir 2. The shut-off valve 6 is optional, but is advantageously included in cases where the variable valve 5 is operable in a range of flow rates where it is always open.

10 Three different forms of the variable valve 5 will now be described. In either of the forms of the therapeutic product delivery device 1 described above, the variable valve 5 may take any of the three different forms described below.

Figs. 3 and 4 show the first form of the variable valve 5, which is arranged as follows.

15 The variable valve 5 comprises a flexible tube 20 having a bore 21 inside the tube 20 that is in fluid communication with the reservoir 2. A portion 22 of the bore 21 forms a variable-sized orifice through which the therapeutic product may flow from the reservoir 2. The flexible tube 20 rests on top of a fixed surface 23 and on a protrusion 24 that protrudes upwardly from the surface 23.

20 The variable valve 5 also comprises an actuator 15 arranged as follows.

The actuator 15 comprises a compressive spring 17 and an SMA wire 18 that are both connected to a fixed body 16 and to an actuated body 19. The actuated body 19 is restricted to move in the vertical direction only as shown by arrow A. The actuated body 19 is arranged adjacent the portion 22 of the bore 21, so that the actuated body 19 locally
25 compresses that portion 22 and changes its size, thereby varying the flow rate of the therapeutic portion therethrough. Specifically, the actuated body 19 is slightly offset from the protrusion 24 so that the flexible tube 20 forms a curved path between the actuated body 19 and the protrusion 24. As a result, the compression of the flexible tube 20 by the actuated body 19 changes the size of the compressed portion 22 by varying the length of
30 the portion 22 of the bore 21 of the flexible tube 20 that is compressed.

The SMA wire 18 contracts when heated by a drive signal supplied thereto, moving the actuated body 19 in a direction that is upwards in Figs. 3 and 4 which increases the size of the orifice formed by the portion 22 of the bore 21. Fig. 3 shows the SMA wire 18 in the fully actuated position (highest temperature) so that the actuated body 19 does not

compress the flexible tube 20 and the bore is at its maximum size (area). The therapeutic product therefore flows at the maximum flow rate through the bore 21 of the flexible tube 20. The maximum flow rate through the valve 5 in this state can be calibrated to provide a maximum required bolus rate of the therapeutic product.

5 The spring 17 is compressive and so acts as a biasing element that resiliently biases the SMA wire 18 so as to change the size of the compressed portion 22 in an opposite sense from the SMA wire 18. The spring 17 may be any resilient element that performs this function, including a coiled spring or a resilient element formed in some other manner, for example as a block of resilient material or a flexure. Fig. 4 shows the SMA wire 18 at the
10 initial position before actuation. The spring 17 exerts enough force on the actuated body 19 so that portion 22 of the bore 21 of the flexible tube 20 is at its minimum size. The portion 22 of the bore 21 of flexible tube 20 is compressed between the actuated body 19 and the protrusion 24 so that the flow rate of the therapeutic product is at the minimum level.

 Fig. 5 shows the cross section of the portion 22 of the bore 21 of the flexible tube
15 20 in the compressed state shown in Fig. 4. The narrow opening of the portion 22 forms the orifice. The minimum flow rate through the compressed tube 20 in this state can be calibrated to provide a minimum required basal rate of the therapeutic product. The actuated body can be placed by the SMA wire 18 at various positions to control the flow rate of the insulin by varying the size of the portion 22 that forms the orifice.

20 Figs. 6 and 7 show the second form of the variable valve 5 which is arranged as follows.

 The variable valve 5 comprises a valve body 30 through which extends a flow path 31 that is in fluid communication with the reservoir 2. The flow path 31 includes an intake tube 32 and a discharge tube 33 which both extend to a diaphragm 35 that is fixed on valve
25 body 30 and extends along the flow path 31. In the configuration shown in Figs. 6 and 7, the diaphragm 35 extends across adjacent openings of the intake tube 32 and the discharge tube 33 separated by a dividing wall 34, but other configurations with the diaphragm 35 extending along the flow path 31 are possible.

 The therapeutic product flows along the flow path 31, entering through the intake
30 tube 32 and exiting through discharge tube 33. An orifice 36 in the flow path 31 is formed adjacent the diaphragm 35, in particular between the diaphragm 35 and the dividing wall 34. The therapeutic product may flow through the orifice 36 from the reservoir 2. The size of the orifice 36 varies in dependence on the deformation of the diaphragm 35 thereby varying the flow rate of the therapeutic product. The variable valve 5 also comprises an

actuator 15 arranged as follows.

The actuator 15 comprises a compressive spring 17 and an SMA wire 18 that are both connected to a fixed body 16 and to an actuated body 19. The actuated body 19 is restricted to move in the vertical direction only as shown by arrow A. The actuated body 19
5 is connected to the diaphragm 35, so that movement of the actuated body 19 deforms the diaphragm 35, which changes the size of the orifice 36 and thereby varies the flow rate of the therapeutic portion through the orifice 36.

The SMA wire 18 contracts when heated by a drive signal supplied thereto, moving the actuated body 19 in a direction that is upwards in Figs. 6 and 7 which increases the size
10 of the orifice 36. Fig. 6 shows the SMA wire 18 in the fully actuated position where the actuator 15 extends the diaphragm 35 to where the orifice 36 is of maximum size to allow the therapeutic product to flow at its maximum rate.

The spring 17 is compressive and so acts as a biasing element that resiliently biases the SMA wire 18 so as to change the size of the orifice 36 in an opposite sense from the
15 SMA wire 18. The spring 17 may be any resilient element that performs this function, including a coiled spring or a resilient element formed in some other manner, for example as a block of resilient material or a flexure. Fig. 7 shows the SMA wire 18 at the initial position before actuation. The spring 17 exerts a force on the actuated body 19 which forces the diaphragm 35 to minimise the size of the orifice 36 so that the the flow rate of
20 the therapeutic product is at the minimum level. In the example, shown in Fig. 7, the diaphragm completely blocks the flow path 31 by sealing the openings of the intake tube 32 and the discharge tube 33 so that the flow of the therapeutic product is stopped.

As an alternative, the orifice 36 could remain open when at its minimum size to provide a minimum flow rate of the therapeutic product. The minimum flow rate of the
25 valve 5 in this state can be calibrated to provide a minimum required basal rate of the therapeutic product.

The actuated body 19 can be placed by the SMA wire 18 at various positions to control the flow rate of the therapeutic product by varying the size of the orifice 36.

Figs. 8 and 9 show the third form of the variable valve 5 which is arranged as
30 follows.

The variable valve 5 comprises a flexible tube 40 having an internal bore 41. The variable valve 5 further includes a rigid tube 43 that is of a smaller diameter than the flexible tube 40. The rigid tube 43 is closed at one end 44, the closed end 44 of the rigid tube 43 is being inserted through the end wall 42 inside the bore 41 of the flexible tube 41,

concentrically with the flexible tube 41. A seal 42 provided at the end of the flexible tube 40 around the rigid tube 43 prevents leakage of the therapeutic product at the interface of the flexible tube 40 and the rigid tube 43. The bore 47 of the rigid tube 43 is similarly completely closed at the end 44 that is inside the flexible tube 43 as shown in Fig. 4A.

- 5 A hole 45 is formed in the sidewall of the rigid tube 43, as further illustrated in Fig. 10 which shows a cross section of the rigid tube 43 at the location of the hole 46.

Thus, a flow path in fluid communication with the reservoir 2 is formed through the bore 41 of the flexible tube 40 and the bore 47 of the rigid tube 43, through the hole 45. An orifice 46 is formed in the flow path and within the flexible tube 40. Specifically, the
10 orifice 46 comprises the hole 45 in the rigid tube 43 and the space between the flexible tube 40 and the rigid tube 43 near the hole 45. The therapeutic product may flow through the orifice 46 from the reservoir 2. The size of the orifice 46 varies in dependence on the deformation of the flexible wall 40 towards the hole 45, thereby varying the flow rate of the therapeutic product.

- 15 The variable valve 5 also comprises an actuator 15 arranged as follows.

The actuator 15 comprises a compressive spring 17 and an SMA wire 18 that are both connected to a fixed body 16 and to an actuated body 19. The actuated body 19 is restricted to move in the vertical direction only as shown by arrow A. The actuated body 19 is aligned with the hole 45, so that actuated body 19 locally compresses the flexible tube 40
20 and changes the size of the orifice 46, thereby varying the flow rate of the therapeutic portion therethrough.

The SMA wire 18 contracts when heated by a drive signal supplied thereto, moving the actuated body 19 in a direction that is upwards in Figs. 8 and 9 which increases the size of the orifice 46. Fig. 8 shows the SMA wire 18 in the fully actuated position such that the
25 actuated body 19 does not deflect the flexible tube 40 and the flow rate of the therapeutic product is at a maximum flow rate. The maximum flow rate through the valve 5 in this state can be calibrated to provide a maximum required bolus rate of the therapeutic product.

The spring 17 is compressive and so acts as a biasing element that resiliently biases the SMA wire 18 so as to change the deflection of the flexible tube 40 in an opposite sense
30 from the SMA wire 18. The spring 17 may be any resilient element that performs this function, including a coiled spring or a resilient element formed in some other manner, for example as a block of resilient material or a flexure. Fig. 9 shows the SMA wire 18 in the initial position before actuation. The spring 17 exerts a force on the actuated body 19 such that the flexible tube 40 is deflected to completely close the orifice 46 by sealing the hole

45 in the rigid tube 43, so that the flow of the therapeutic product is stopped.

As an alternative, the orifice 46 could remain open when at its minimum size to provide a minimum flow rate of the therapeutic product. The minimum flow rate through the compressed tube 20 in this state can be calibrated to provide a minimum required basal
5 rate of the therapeutic product.

The actuated body can be placed by the SMA wire 18 at various positions to control the flow rate of the insulin by varying the orifice size.

In each of the above forms of the valve 5, it is understood that the length of the SMA wire 18 can be varied by varying the temperature of the wire and the force produced
10 by the SMA wire 18 is enough to overcome any other forces (such as the force of the compressive spring 17 and fluid pressures) so that the SMA wire 18 can actuate the actuated body 19. The SMA wire 18 resets to its original length at ambient temperature under the action of the compression spring 17.

In each of the above forms of the valve 5, the actuator 15 is configured to change
15 the size of the respective orifice within a range. The range may be of at least two orders of magnitude, preferably at least three orders of magnitude, which may accommodate the desired range for a given therapeutic product. In the case of insulin, the range may be from a lower limit at or below 0.05 U/hour to an upper limit at or above 20 U/hour, corresponding to a lower limit at or below 1.735 µg/hour to an upper limit at or above 714
20 µg /hour.

In general in any form of the valve 5, the range may extend to the orifice being entirely closed so that the minimum flow rate of the therapeutic product is zero, or the range may extent within a range in which the orifice is always open so that the minimum flow rate of the therapeutic product is greater than zero.

25 The actuator 15 described above comprises an SMA wire 18 that is used to move the actuated body 19 and thereby change the size of the respective orifice in each form of the valve 15. However, the actuator 15 may be configured in other ways. By way of non-limitative example, Figs. 11 and 12 show alternative forms of the actuator 15 which may be employed in any of the above forms of the valve 5.

30 In the alternative form of the actuator 15 shown in Fig. 11, the SMA wire 18 is configured to apply a force to the actuated body 19 in the opposite direction, i.e. to minimise the size of the orifice when the SMA wire 18 is fully actuated. In this case, the spring 17 is in tension so that it resiliently biases the SMA wire 18 so as to change the size of the orifice in an opposite sense from the SMA wire 18.

In the alternative form shown in Fig. 12, the actuator 15 comprises an additional SMA wire 50 also connected between the fixed body 16 and the actuated body 19 but configured to change the size of the orifice in an opposite sense from the SMA wire 18 in the actuator 15 described above. This is therefore an arrangement in which the SMA wires 18 and 50 are opposed.

The actuator 15 described above uses an SMA wire 18 is a form of electrically driven actuator. However, the use of SMA is not essential. Alternatively, the actuator 15 could be an alternative form of electrically driven actuator configured to change the size of the orifice.

Fig. 13 illustrates the control system 60 of the therapeutic product delivery device 1. The control system 60 is connected to the SMA wire 18 and supplies a drive signal to the SMA wire 18 that electrically drives the actuator 15. The control system 60 may be implemented in any suitable manner, for example in an integrated circuit chip. The control system 60 may include a drive circuit 61 arranged to generate the drive signal, and a control unit 62 that is arranged to control the drive circuit 61. The drive circuit 61 may be implemented by suitable electronic components. The control unit 62 may be implemented by a processor executing an appropriate program. The control unit 62 controls the power of the drive signal supplied by the circuit 61. For example, the drive signal may be a pulse-width modulated signal whose pulse-width is controlled by the control unit 61 to vary the power of the drive signal and thereby control the actuator 15.

The control system 60 may further include a resistance measurement circuit 63 that is connected to the SMA wire 18 and measure the resistance thereof. In that case, a measure of the resistance of the SMA wire 18 output from the resistance measurement circuit 63 is supplied to control unit 62 which uses it as a feedback signal to control the power of the drive signal, for example to cause the actuator 15 and hence the valve 5 to deliver a controlled flow rate of the therapeutic product.

The control system 60 may control the flow rate in whatever manner is desired for the therapeutic product. In cases where the therapeutic product is desired to be variably delivered at a basal rate and at times at an increased bolus rate, for example where the therapeutic product is insulin, the control system 60 may drive the actuator 15 to cause the valve 5 to deliver a flow rate of the therapeutic product that varies between the basal rate and the bolus rate.

Claims

1. A therapeutic product delivery device for delivering metered volumes of a therapeutic product, the device comprising:
 - 5 a pressurised reservoir containing the therapeutic product, the therapeutic product being a fluid;
 - a variable-sized orifice in fluid communication with the reservoir for flow of the therapeutic product through the orifice; and
 - an electrically driven actuator configured to change the size of the orifice to vary
 - 10 the flow rate of the therapeutic product.
2. A therapeutic product delivery device according to claim 1, wherein the actuator comprises a shape memory alloy wire.
- 15 3. A therapeutic product delivery device according to claim 2, further comprising an additional shape memory alloy wire configured to change the size of the orifice in an opposite sense from the first mentioned shape memory alloy wire.
4. A therapeutic product delivery device according to claim 2, further comprising a
- 20 biasing spring, configured to resiliently bias the shape memory alloy wire so as to change the size of the orifice in an opposite sense from the shape memory alloy wire.
5. A therapeutic product delivery device according to any one of the preceding claims, comprising a flexible tube, the variable-sized orifice being formed inside the flexible tube,
- 25 and the actuator being configured to locally compress the flexible tube so as to change the size of the orifice to vary the flow rate of the therapeutic product.
6. A therapeutic product delivery device according to claim 5, wherein the orifice is a portion of a bore of the flexible tube, the actuator being configured to locally compress the
- 30 flexible tube so as to change the size of the orifice to vary the the flow rate of the therapeutic product.
7. A therapeutic product delivery device according to claim 6, wherein the actuator is configured to locally compress the flexible tube to change the size of the orifice by varying

the length of the portion of the bore of the flexible tube that is compressed.

8. A therapeutic product delivery device according to claim 5, further comprising a rigid tube with which the flexible tube is concentric, the rigid tube having a hole, the orifice
5 being formed between the flexible tube and the hole in the rigid tube.

9. A therapeutic product delivery device according to any one claims 1 to 4, further comprising a valve body defining a flow path in fluid communication with the reservoir, and a diaphragm fixed to the valve body along the flow path, the orifice being adjacent the
10 diaphragm and the actuator being configured to deform the diaphragm so as to change the size of the orifice.

10. A therapeutic product delivery device according to any one of the preceding claims, wherein the actuator is configured to change the size of the orifice within a range extending
15 to the orifice being entirely closed.

11. A therapeutic product delivery device according to any one of the preceding claims, wherein the actuator is configured to change the size of the orifice within a range in which the orifice is always open.
20

12. A therapeutic product delivery device according to any one of the preceding claims, further comprising an additional valve configured to close the flow of the therapeutic product from the reservoir.

25 13. A therapeutic product delivery device according to any one of the preceding claims, wherein the pressurised reservoir comprises a syringe comprising a plunger and a spring pushing on the plunger.

14. A therapeutic product delivery device according to any one of claims 1 to 13,
30 wherein the pressurised reservoir comprises a container having a flexible wall, and a spring pushing against the flexible wall.

15. A therapeutic product delivery device according to any one of the preceding claims, wherein the therapeutic product is a liquid.

16. A therapeutic product delivery device according to any one of the preceding claims, wherein the therapeutic product comprises insulin.

5 17. A therapeutic product delivery device according to claim 16, wherein the actuator is arranged to change the size of the orifice to vary the flow rate across a range from a lower limit at or below 1.735 µg/hour to an upper limit at or above 714 µg /hour.

18. A therapeutic product delivery device according to any one of the preceding claims,
10 wherein the actuator is arranged to change the size of the orifice to vary the flow rate across a range of at least two orders of magnitude, preferably at least three orders of magnitude.

19. A therapeutic product delivery device according to any one of the preceding claims, further comprising a control system configured to electrically drive the actuator.

15

20. A therapeutic product delivery device according to claim 19, wherein the actuator comprises an SMA wire, and the control system is configured to measure the resistance of the shape memory alloy wire and to electrically drive the shape memory alloy wire using feedback of the measured resistance to deliver a controlled flow rate of the therapeutic
20 product.

21. A therapeutic product delivery device according to claim 19 or 20, wherein the control system is configured to electrically drive the actuator to deliver a flow rate of the therapeutic product that varies between a basal rate of the therapeutic product and an
25 increased bolus rate of the therapeutic product.

1/5

Fig. 1

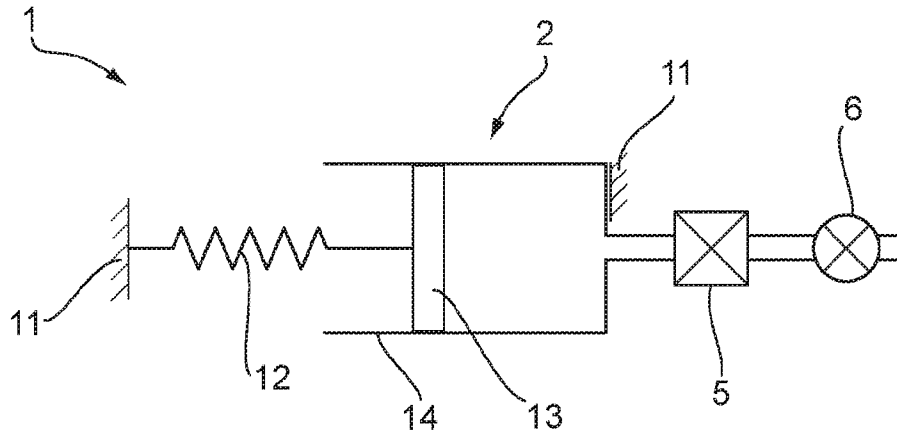


Fig. 2

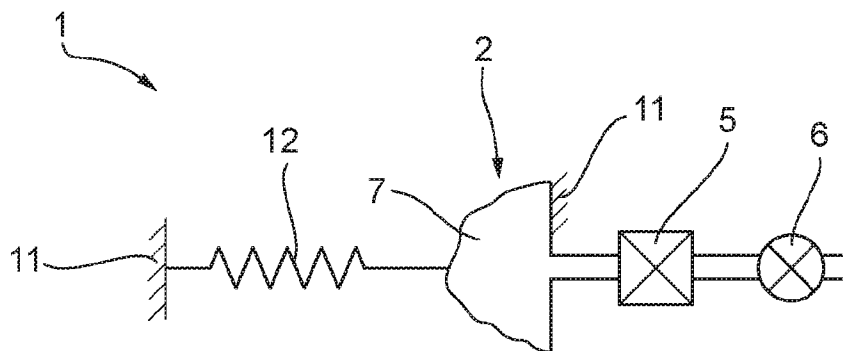
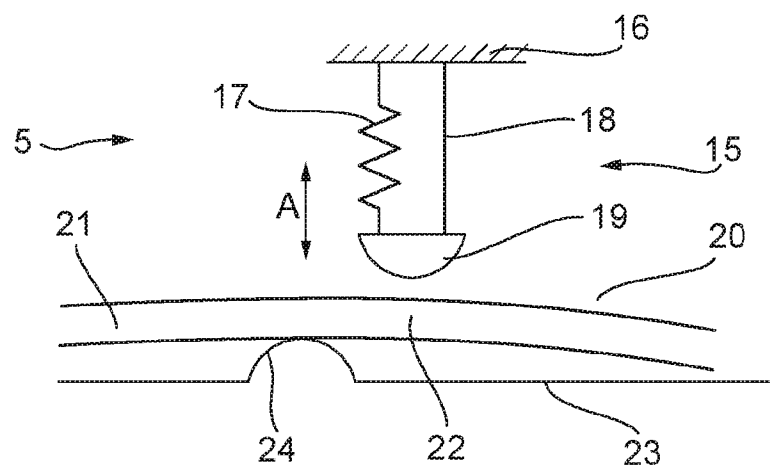


Fig. 3



2/5

Fig. 4

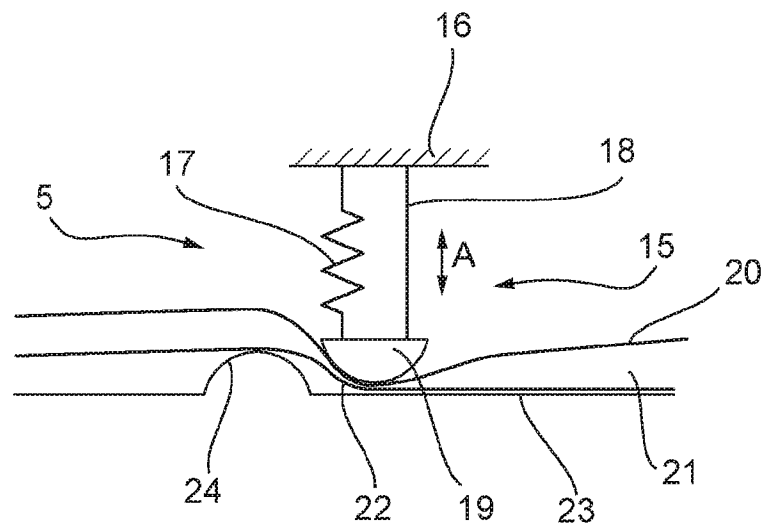
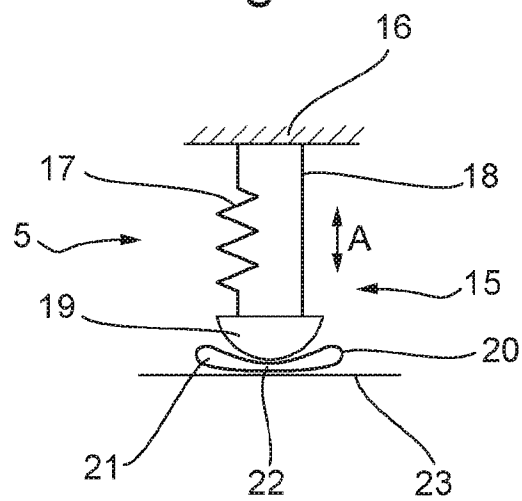


Fig. 5



3/5

Fig. 6

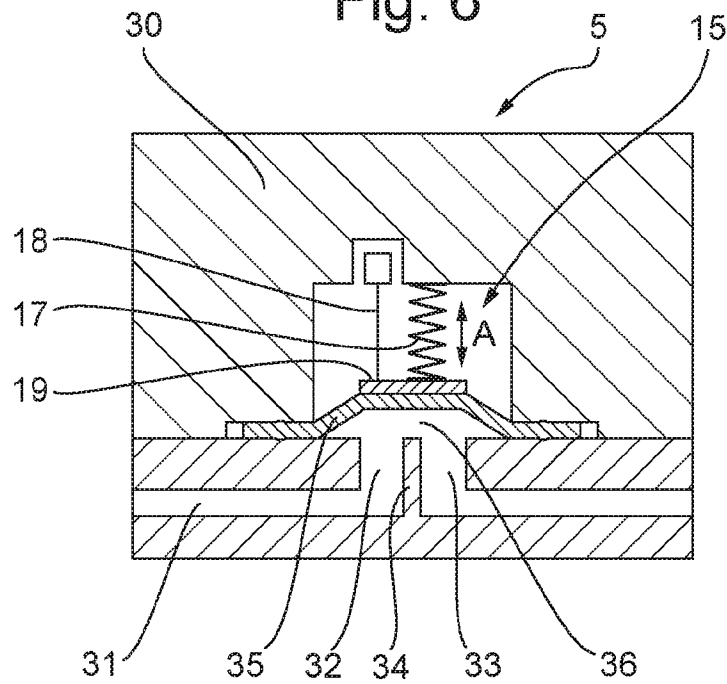
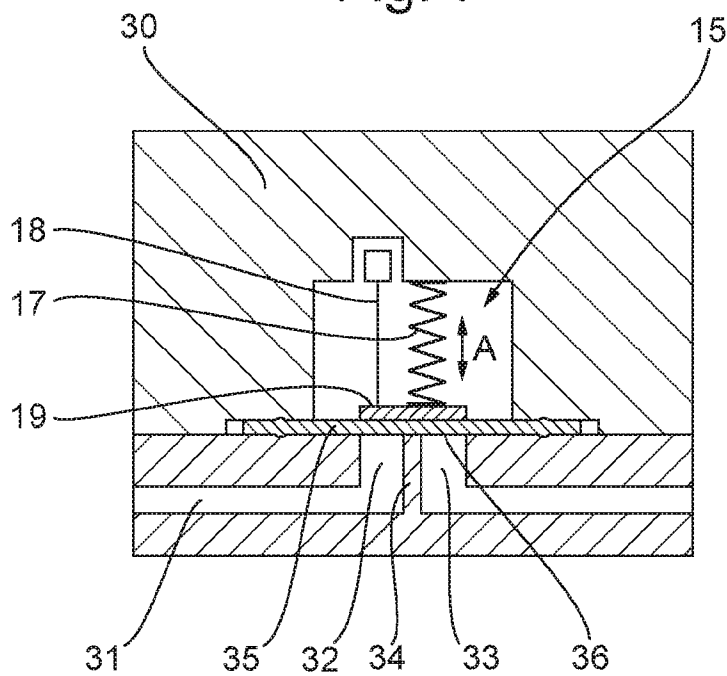
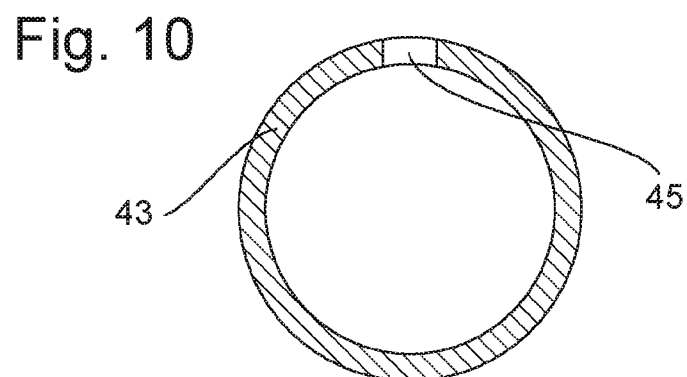
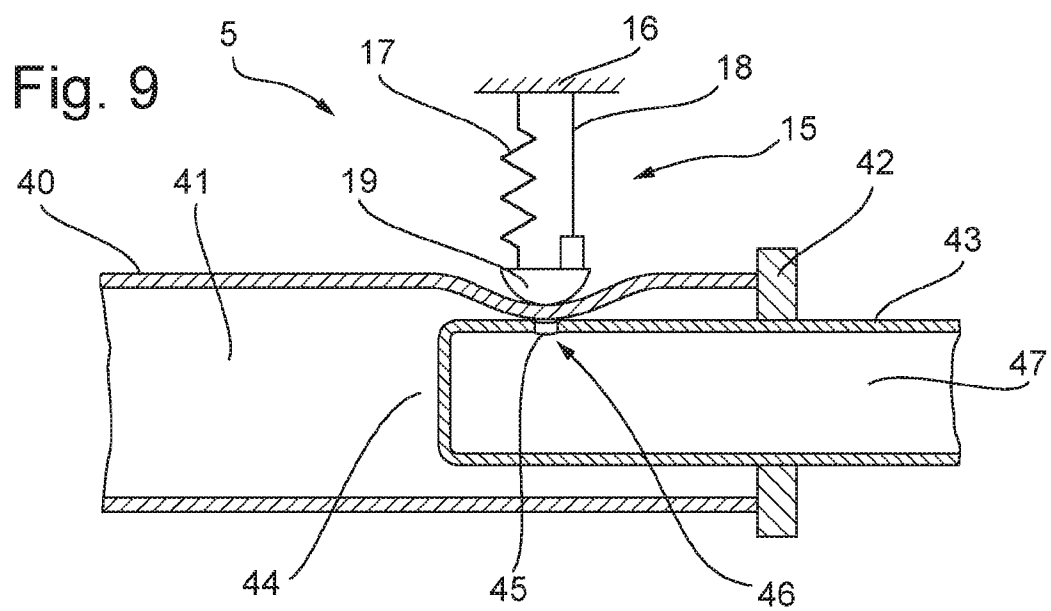
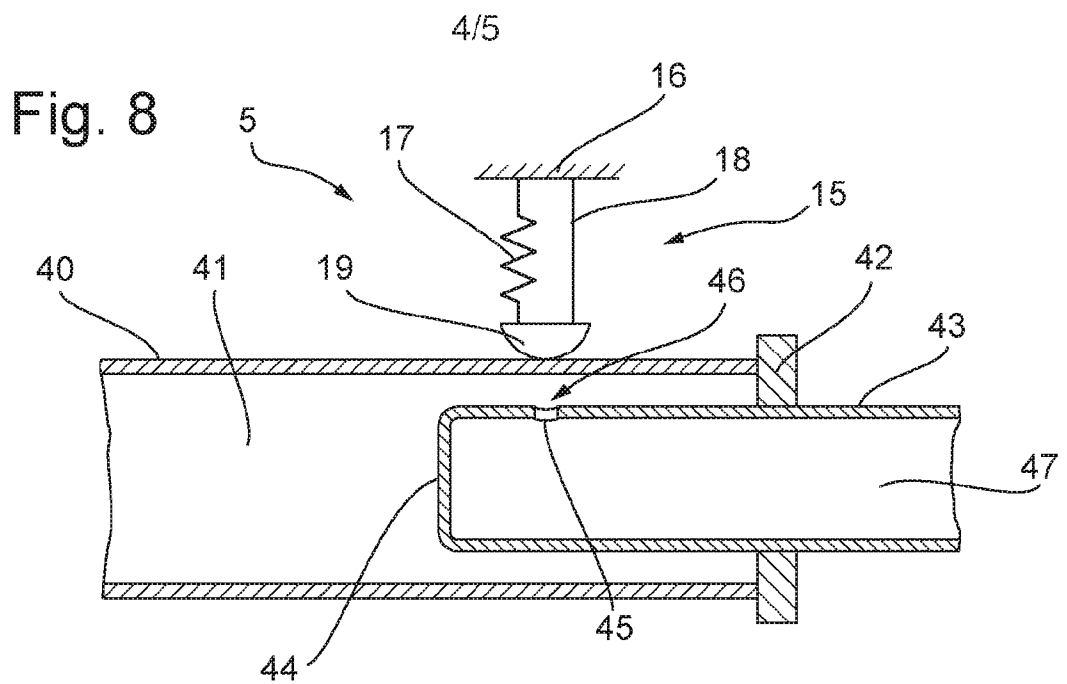


Fig. 7





5/5

Fig. 11

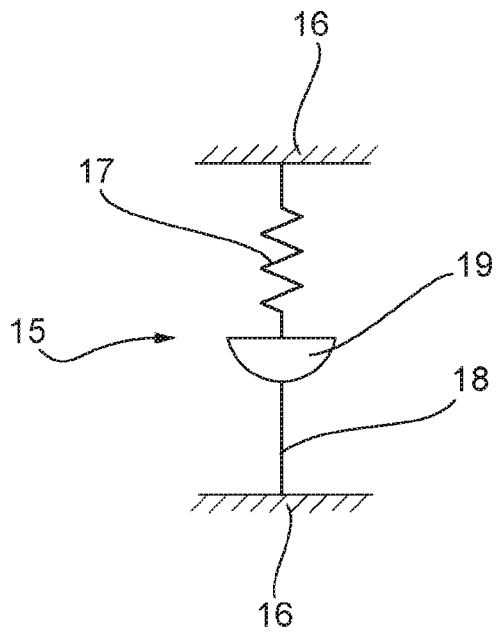


Fig. 12

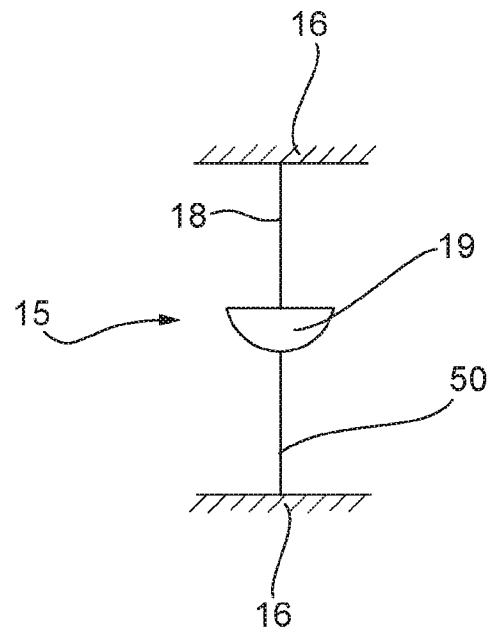
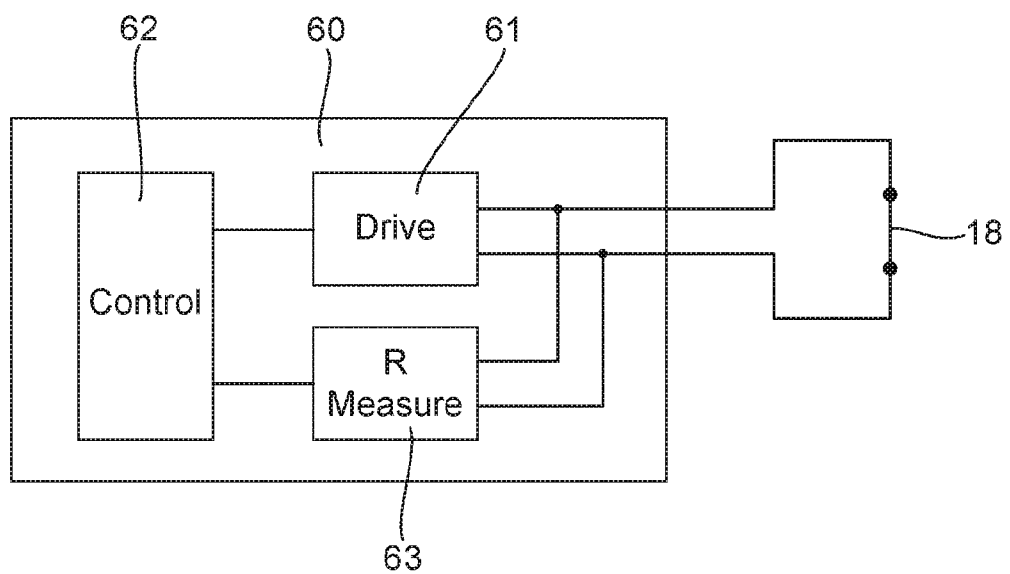


Fig. 13



INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2017/053859

A. CLASSIFICATION OF SUBJECT MATTER INV. A61M5/168 A61M5/142 A61M5/145 A61M5/148 ADD.		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols) A61M		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 110 685 A1 (ALCHEMIA [US]) 13 June 1984 (1984-06-13) figures 1, 2, 4a page 1, lines 2-9 page 3a, lines 19-21 page 4, lines 4-5 page 10, line 28 - page 11, line 3 page 12, lines 1-3 -----	1,2,4-6, 10-12, 15-21
X	US 2009/113996 A1 (WANG JONG H [US] ET AL) 7 May 2009 (2009-05-07) figures 9-11, 16 paragraphs [0045], [0073] ----- -/--	1-7,10, 11, 13-18,21
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
16 February 2018		26/02/2018
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Herz, Markus

INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2017/053859

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2002/107472 A1 (THOMPSON DAVID L [US] ET AL) 8 August 2002 (2002-08-08) figure 4 paragraphs [0007], [0008], [0032], [0033] -----	1-4,7-21
X	EP 2 698 178 A2 (BECTON DICKINSON CO [US]) 19 February 2014 (2014-02-19) figure 6 paragraphs [0032], [0033], [0073] -----	1-6,9-21

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2017/053859

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0110685	A1	13-06-1984	CA 1224860 A 28-07-1987
		DE 3372918 D1 17-09-1987	
		EP 0110685 A1 13-06-1984	
		JP H0622636 B2 30-03-1994	
		JP S59151966 A 30-08-1984	

US 2009113996	A1	07-05-2009	NONE

US 2002107472	A1	08-08-2002	NONE

EP 2698178	A2	19-02-2014	CA 2823345 A1 15-02-2014
		CN 203647799 U 18-06-2014	
		EP 2698178 A2 19-02-2014	
		JP 2014050686 A 20-03-2014	
		US 2014052096 A1 20-02-2014	
