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(54) Title: MEDICAMENT DISPENSER

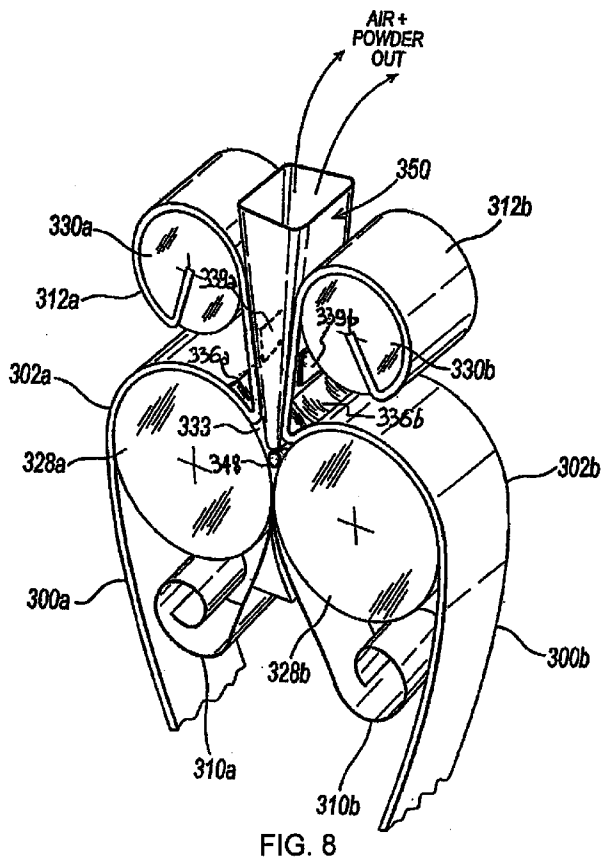

FIG. 8

(57) Abstract: The invention relates to a medicament dispenser with a medicament pack having a first structure (310a, 310b) and a second structure (312a, 312b) which is intended to be separated from said first structure for releasing medicament from locations enclosed by the first and second structures, said second structure having a laminated construction and comprising a metallic and a non-metallic layer, said medicament dispenser comprising: (i) an internal dispensing mechanism (330, 328) for separating said second and first structure to expose said medicament locations and advance the separated first and second structures on respective first and second paths in the dispenser; and (ii) an outlet at which a user is able to receive medicament from the exposed medicament locations, wherein the dispenser is provided with a fault detector for detecting when medicament is potentially not being released, said fault detector comprising a sensor (339a, 339b) associated with said second path, said sensor detecting an absence of said metallic layer in said second path and producing an output signal based on said detected absence.

WO 2009/003989 A1

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Medicament Dispenser

Field of the Invention

The present invention in one aspect relates to a fault detector for use in a medicament dispenser comprising a dispensing mechanism. The present invention in a further aspect relates to a locking mechanism for use in such a device. The present invention can be used in an inhaler comprising a strip having a releasable product therein, such as a dry powder medicament. The medicament may be, for example, for treatment of bronchial, tracheal or lung disorders, such as asthma. Medicaments for treatment of other disorders may also be dispensed by such inhalers.

Background of the Invention

The use of inhalation devices in the administration of medicaments, for example in bronchodilation therapy, is well known. Such devices may comprise a body or housing within which one or two strips of medicament from one or two source spools are located. The strip may comprise a base sheet having a number of pockets defined therein containing a dose of medicament in powder form, and a cover sheet provided thereto.

In such arrangements, the feeding of the strip to a mouthpiece of the inhaler device is typically achieved by a strip feeding mechanism that usually comprises a series of gears and/or spools within the device. A suitable peeling mechanism is positioned to peel apart a base sheet and a cover sheet of a pocket at an opening station of the inhaler device. The peeling mechanism typically includes a sheet driver for pulling apart a cover sheet from a base sheet of a pocket that has been received at the opening station. Lead spools are provided for winding up the spent strip components, i.e. the separated cover and base sheets. The medicament contained in the pocket is thereby made available for inhaled delivery to the patient.

The cover sheet usually includes a metal layer and the base sheet usually includes a metal layer. The cover sheet also usually comprises an outermost paper layer which overlies the metal layer.

A potential problem that can be encountered is that the cover sheet may become damaged during use.

In WO-A-2007/038488 there is disclosed a cover sheet constructed to resist damage during use. The entire content of this International application, and its counterpart US national phase application, is incorporated herein by reference.

Another solution to the above potential problem has been proposed in Applicant's PCT Patent Application WO2006/123110 which describes in some embodiments a fault indicator for a strip advancement mechanism in which an element of a fault sensing portion bears against a cover sheet of a strip. As a result of a loss of tension in the cover sheet due to the cover sheet breaking, tearing, stretching or failing, the bias of the element causes the element to move into a fault indicating position either immediately or upon one or more further activations of the strip advancement mechanism. The fault indicator may provide a visual indication of the fault, such as brightly coloured indicia.

A further fault indicator is disclosed in Applicant's co-pending UK patent application No. 06 228 27.4, filed 15 November 2006.

If the cover sheet were to delaminate, parts of the cover sheet would not be peeled off the base sheet and it may be that at least one of the layers of the cover sheet is peeled off (e.g. just the paper layer), with the rest of the cover sheet (e.g. comprising the metal layer) remaining attached to the base sheet. Further dispensing of medicament may thus not be possible despite the strip continuing to be fed by the pulling of the base sheet (which includes the attached cover sheet portion) and the delaminated layer(s) through the inhaler device.

It would be desirable to provide a way of detecting damage to the strip of an inhaler device, including delamination, to provide an indication to the patient

of such fault. It would also be desirable to provide an improved locking mechanism for a dispensing mechanism when such a fault is detected. It would also be desirable to provide such benefits to a medicament dispenser *per se* having a medicament pack comprising a pair of structures which are intended to be separated from one another to enable release of medicament.

Summary of the Invention

In accordance with one aspect of the present invention, there is provided a medicament dispenser for dispensing medicament from a medicament pack, said medicament pack having a first structure, a second structure which is secured to said first structure and which is intended to be separated from said first structure to enable release of medicament from spaced-apart medicament locations enclosed by the first and second structures, said second structure having a laminated construction and comprising a metallic layer and a non-metallic layer, said medicament dispenser comprising:

(i) an internal dispensing mechanism for separating said second structure from the first structure to expose said medicament locations and advance the separated first and second structures on respective first and second paths in the dispenser; and

(ii) an outlet at which a user is able to receive medicament from the exposed medicament locations,

wherein the medicament dispenser is provided with a fault detector adapted to detect a fault condition in which medicament is potentially not being released, said fault detector comprising a sensor associated with said second path, said sensor being capable of detecting an absence of said metallic layer in said second path and being adapted to produce an output signal based on said detected absence.

The invention provides a medicament dispenser including a fault detector for detecting a fault in a cover sheet of a medicament carrier, including delamination of the cover sheet.

In one embodiment, the fault detector comprises a radiation source, which is preferably a light source, the detection of a fault condition in the cover sheet being detected on the basis of the amount of light from the light source which is transmitted through the separated cover sheet and sensed by the sensor.

In a preferred embodiment, the fault detector is used in a medicament dispenser comprising two medicament strips. In that case, the fault detector preferably comprises a radiation source and two sensors, the light from the radiation source being directed in the outlet of the dispenser which acts as a light guide to guide the light towards the input regions of the two sensors in front of which each of the separated cover sheet of a respective medicament strip is guided.

In accordance with a second aspect of the present invention, there is provided a medicament dispenser for dispensing medicament from a medicament pack, said medicament pack having a first structure, a second structure which is secured to said first structure and which is intended to be separated from said first structure to enable release of medicament from spaced-apart medicament locations enclosed by the first and second structures, said medicament dispenser comprising:

(i) an internal dispensing mechanism for separating said second structure from the first structure to expose said medicament locations and advance the separated first and second structures on respective first and second paths in the dispenser; and

(ii) an outlet at which a user is able to receive medicament from the exposed medicament locations,

wherein the medicament dispenser is provided with a fault detector adapted to detect a fault condition,

said medicament dispenser being further provided with a locking mechanism, said locking mechanism being adapted to move in response to an electrical drive input from a non-locking position to a locking position in the event that said fault condition is detected.

The invention provides a medicament dispenser including a fault detector for detecting a fault in a cover sheet of a medicament strip and an electrically-driven locking mechanism which is arranged, when a fault is detected, to 'lock out' further use of the medicament dispenser by, for example, locking an element of the internal dispensing mechanism of the medicament dispenser. The patient is thereby given a clear message that the medicament dispenser has failed and that a replacement must be obtained.

Such a fault may be the cover sheet delaminating, breaking, tearing, stretching or failing. The fault detector preferably includes an arrangement capable of producing electrical drive signals, preferably comprising a radiation source and at least one radiation sensor.

In one embodiment, the locking mechanism comprises a locking element, for example a pin associated with the cover sheet driver, which blocks further actuation of the strip advancement mechanism and thereby provides an indication of a fault to a user.

In a preferred embodiment, the locking element is maintained in a non-locking position by an actuator which releases the locking element and a biasing mechanism to move it to a locking position in the event that a fault in a cover sheet is detected.

Further features, aspects and advantages of the invention will become apparent from the claims and the following description of preferred embodiments of the invention, given by way of example only, which is made with reference to the accompanying drawings.

Brief Description of the Drawings

Figure 1 shows a perspective view of a medicament pack suitable for use with a medicament dispenser device in accordance with an embodiment of the present invention, and as used in the illustrated embodiments hereinafter described;

Figure 2 shows a schematic sectional view of the base unit of a medicament dispenser device in accordance with an embodiment of the invention, the medicament dispenser device comprising a pair of the medicament packs of Figure 1;

Figure 3 shows a cut-away view of an assembly of the mouthpiece and the manifold of another medicament dispenser device in accordance with an embodiment of the invention;

Figures 4a to 4c show in side view the medicament dispenser, in accordance with the embodiment of Figure 3, in different configurations corresponding to sequential steps for preparing the medicament dispenser for use, where the dispenser is shown absent its outer housing;

Figure 5a shows in exploded perspective view the gear mechanism of the medicament dispenser in accordance with the embodiment of Figure 3;

Figure 5b shows in perspective view the internal dispensing mechanism and the medicaments packs of the medicament dispenser in accordance with the embodiment of Figure 3;

Figures 6a to 6c show in side view details of the gear mechanism when prepared for use in sequential steps corresponding to those of Figures 4a to 4c;

Figure 7 shows in side view a detail of a ratchet "anti return" mechanism of the medicament dispenser in accordance with the embodiment of Figure 3;

Figure 8 shows a schematic perspective view of the base unit of Figure 2 comprising a manifold and a fault detector in accordance with an embodiment of the present invention;

Figure 9 shows a schematic cross-sectional side view of the manifold of Figure 3 showing its "in use" relationship with the medicament packs and a fault detector in accordance with an embodiment of the present invention;

Figure 10 is a schematic diagram showing an electronic circuit for a medicament dispenser device in accordance with an embodiment of the present invention, as may be used for the fault detector of Figures 8 or 9;

Figure 11 is a schematic diagram showing an electronic circuit of a medicament dispenser device in accordance with a further embodiment of the present invention, as may be used for the fault detector of Figures 8 or 9;

Figures 12a to 19b are schematic diagrams of a locking mechanism of a medicament dispenser device in accordance with various different embodiments of the present invention; and

Figures 20a to 20c show schematic sequential views of an arrangement for powering an electrical circuit of a medicament dispenser in accordance with an embodiment of the present invention.

Detailed Description of the Invention

Figure 1 shows a medicament pack 100 for use with a medicament dispenser device in accordance with an embodiment of the present invention. The medicament pack 100 is in the form of a flexible elongate strip 102 defining a plurality of spaced-apart locations in the form of pockets 104 each of which contains a dose (or portion thereof) of inhalable medicament powder. The strip 102 is sufficiently flexible to be wound into a roll, as shown in Figure 1. The flexible elongate strip 102 comprises a pair of structures which are intended to be separated from one another to enable release of medicament. The strip 102 comprises a first structure which is a base sheet 110 in which blisters 106 are formed, by cold forming or deep drawing, to define the pockets 104 and a second structure which is a cover sheet 112. The cover sheet 112 is secured to the base sheet 110 in that it is hermetically sealed to the base sheet 110, except in the region of the blisters 106, to hermetically cover the pockets 104. The hermetic sealing of the base and cover sheets 110, 112 is such that the base and cover sheets 110, 112 are able to be peeled apart to open the pockets 104 for access to the medicament powder. The sheets 110, 112 are sealed to one another over their whole width except for the leading end portions 114, 116 where they are preferably not sealed to one another at all.

Various known techniques can be employed to join the cover and base sheet and hence to seal the blisters of the peelable blister strip. Such methods include adhesive bonding, hot metal bonding, hot metal welding, radio frequency welding, laser welding, ultrasonic welding and hot bar sealing. The cover sheet and base sheet of the peelable blister strip are particularly sealable by 'cold form' sealing methods, which are conducted at lower temperatures than conventional heat sealing methods. Such 'cold form' sealing methods are of particular utility where the drug or drug formulation for containment within the blister is heat sensitive (e.g. degrades or denatures on heating). Suitable 'cold form' sealing methods are conducted at a temperature in the range of 150-250°C.

In one embodiment, the medicament pack comprises a peelable blister strip, the cover 112 and base 110 sheets of which have a laminated construction. In preferred embodiments, the laminate comprises material selected from the group consisting of metal foil, organic polymeric material and paper. Suitable metal foils include aluminium or tin foil having a thickness of from 5 to 100μm, preferably from 10 to 50μm, more particularly 20 to 30μm. Suitable organic polymeric materials include polyethylene, polypropylene, polyvinyl chloride and polyethylene terephthalate.

The cover sheet 112 comprises at least the following successive layers, including a metallic layer and a non-metallic layer: (a) paper; adhesively bonded to (b) polyester; adhesively bonded to (c) aluminium foil; that is coated with a heat seal lacquer for bonding to the base sheet. The thickness of each layer may be selected according to the desired properties but is typically of the order of from 5 to 200 micron, more particularly from 10 to 50 micron. The base sheet 110 comprises at least the following successive layers: (a) oriented polyamide (OPA); adhesively bonded to (b) aluminium foil; adhesively bonded to (c) a third layer comprising a polymeric material (e.g. polyvinyl chloride). Other constructions, however, may be used for the cover and/or base sheets.

The pockets 104 are identical to one another and, with the exception of a test pocket 108 at the leading end of the strip 102, are equi-spaced along the strip length. The pockets 104 are elongate and extend transversely with respect to the length of the strip 102. This is convenient in that it enables a large number of pockets 104 to be provided in a given strip length. The strip 102 may, for example, be provided with thirty, sixty or one hundred pockets 104, but it will be understood that the strip 102 may have any suitable number of pockets 104.

In embodiments of the present invention, such as hereinafter described with reference to the Figures of drawings, plural such medicament packs 100 are employed in a single medicament dispenser device. Each medicament pack may provide the component medicament dose portions of a combination medicament product. Alternatively, a limited number (e.g. one) of the medicament packs may contain a medicament powder formulation with the other(s) being empty or containing a non-medicament powder formulation (e.g. lactose), wherein the limited number of medicament packs provide the medicament product. This may be the case where not all the packs are needed for delivery of the medicament product, e.g. a monotherapy. A further alternative is that each pack, or a limited number of packs, contain the same medicament powder formulation, wherein in the latter case the others pack(s) is empty, or containing a non-medicament powder formulation, and/or containing one or more different medicament powder formulations.

Preferably, the medicament dispenser is designed to receive from two to four such elongate form medicament packs, more preferably two such medicament packs. Each such medicament pack 100 may be of the same size and/or contain the same dose amount (e.g. volume or mass) or in alternative embodiments, packs of different sizes and/or containing different dose amounts may be employed in combination. It will be appreciated that the medicament dispenser of the present invention may alternatively be designed to receive a single elongate medicament pack 100.

Figure 2 is a schematic view of a hand-held, hand-operable medicament dispenser device, within which an embodiment of the invention operates, which is in the form of a dry powder inhaler. The medicament dispenser device is provided with two medicament packs 100a, 100b in the form of the flexible blister strips 102a, 102b described above with reference to Figure 1. The flexible blister strips 102a, 102b are identical, the pockets in each being of the same shape and size and being equi-spaced along the strip length. The flexible blister strips 102a, 102b each comprise a pair of structures which are intended to be separated from one another to enable release of medicament.

In this particular embodiment, a first one of the strips 102a contains the same medicament powder in each of its pockets, with the amount of active ingredient(s) also being the same in each pocket of that strip. The other strip 102b similarly contains a common medicament powder in each of its pockets, each such pocket again having the same amount of active ingredient(s) therein. The medicament powder in each strip may contain a single active ingredient or a mixture of active ingredients. However, in this embodiment the medicament powder in one strip contains at least one active ingredient not in the other strip. As to be detailed further hereinafter, on operation of the medicament dispenser device, a pocket of each blister strip 102a, 102b is peeled open to expose the different medicament powders therein. The patient then inhales from the mouthpiece to simultaneously inhale the powders from the open pockets 104a, 104b of the strips 102a, 102b. The patient thus receives a fixed metered dose of medicament powder of which the different medicament powders from each open pocket 104a, 104b make up respective dose portions. The content of each strip 202a, 202b may be varied, however, as discussed earlier.

Figure 2 illustrates a base unit 119 of a medicament dispenser device holding a first and a second medicament-containing blister strip 102a, 102b which are positioned within respective left and right chambers 123a, 123b of the base unit 119. Each blister strip 102a, 102b engages a respective multi-pocket index wheel 128a, 128b, and successive pockets are thereby guided towards a

common opening station 133. The index wheels 128a, 128b are rotatably coupled. At the opening station 133, the cover sheet 112a, 112b and base sheet 110a, 110b parts of each strip 102a, 102b are peelably separable about a respective separator 136a, 136b to deliver powder from each respective opened pocket thereof to an outlet, which in embodiments takes the form of a manifold 250; 450 which is shown in Figure 3 and Figure 9. The manifold locates at manifold-receiving station 141. The manifold guides airflow towards one or more opened blister pocket(s) for liberating the powder contained therein and subsequently guides that liberated powder to a mouthpiece 226 (shown in Figure 3) for inhalation by a patient. Medicament from an opened pocket of the one or more medicament packs may thus, be channelled via the manifold to the mouthpiece 226.

The separated cover sheet 112a, 112b and base sheet 110a, 110b parts of each strip 102a, 102b are advanced on respective first and second paths in the dispenser. The resulting separated empty base sheet 110a, 110b coils about a base sheet take-up spindle (not shown) in respective base take-up chambers 132a, 132b. The used separated cover sheet 112a, 112b is fed over its respective separator 136a, 136b and coiled about a cover take-up spindle 130a, 130b in the cover take-up chamber 131a, 131b.

A base sheet anchor (not shown) anchors the end of each respective base sheet 110a, 110b in its chamber 132a, 132b. The looped end of each cover sheet 112a, 112b of each medicament pack is received by an upwardly standing hook (not shown) which is part of the cover take-up spindle 130a, 130b.

Figure 3 shows a cut-away view of a medicament dispenser device, within which an embodiment of the invention operates, with its mouthpiece 226 and manifold 250 (the manifold is also shown in Figure 9, labelled with reference number '450'). The reference numbers of similar components to Figures 1 and 2 have been incremented by 100, and the relevant description of those components above should be taken to apply.

In more detail, the housing comprises mating first 220a and second 220b shell cover parts, which in combination act to house the dispenser device mechanisms thereof. The manifold 250 is received by the first shell cover part 220a such that a lip defining an inlet 253 to a chimney 252 is received within an inner wall of the first shell cover part 220a which defines the air inlet grille 270.

The air inlet grille 270 in the first shell cover part 220a is covered by the mouthpiece cover 230 when in a closed position (as shown in Figure 4a), part-uncovered when the mouthpiece cover is in a part-opened position (as shown in Figure 4b) and fully revealed when the mouthpiece cover is in an open position (as shown in Figure 4c).

In use, the air inlet grille 270 allows air to pass from outside the medicament dispenser device into the manifold 250 via the chimney inlet 253 to the chimney 252 in response to inhalation by the patient through the mouthpiece 226, as indicated schematically by arrow 283 in Figure 3. Notably, this air inlet grille 270 provides the sole intended point of entry of air from the outside into the medicament dispenser device upon patient inhalation at the mouthpiece 226. More particularly, the air inlet grille 270 provides the sole entry point for air outside the dispenser device to pass into the manifold 250 upon patient inhalation on the mouthpiece 226.

The manifold 250 is also received by second shell cover part 220b such that its protruding foot 255 sits within the manifold-receiving cavity thereof. The manifold 250 is provided with a pair of wings (not shown) which are assembly features which enable the manifold 250 to be pushed onto the mouthpiece 226.

As may also be seen by reference to Figure 3, the manifold 250 has a particular inner structure in which chimney 252 locates above a chamber 260 and partly shares a common wall 259 therewith, which common wall 259 forms the bottom wall of the chimney 252 and part of the top wall of the chamber 260. The terms “above”, “bottom” and “top” are only used to describe the relative

positioning of features in the manifold 250 in the orientation that the manifold 250 is shown in Figure 3.

The chimney 252 has the chimney inlet 253 and a pair of chimney exits 254a, 254b (only one shown). In use, the chimney 252 directs inward airflow (as exclusively received through the air inlet grille 270 on patient inhalation at the mouthpiece 226) from the chimney inlet 253 to the pair of chimney exits 254a, 254b. The chamber 260 has a pair of chamber inlets 273a, 273b (only one shown) and a chamber exit 274. A more detailed description of the medicament dispenser device, including of the chimney exits 254a, 254b and both chamber inlets 273a, 273b, is provided in WO-A-2007/068900 and WO-A-2007/068896 which (together with their US national phase counterparts) are incorporated herein by reference in entirety.

The pair of chimney exits 254a, 254b and pair of chamber inlets 273a, 273b are both defined by a pair of circular holes, in this particular embodiment of diameter about 3mm, and each hole is provided with a respective cruciform 251, 261. Each chimney exit 254a, 254b is paired with one of the chamber inlets 273a, 273b by positioning them adjacent to one another. The mouthpiece 226 is provided to the chamber exit 274 and snap-mounts thereto via snap-mounting feature 276.

Figures 4a to 4c show in side view a medicament dispenser, within which an embodiment of the invention operates, in different configurations corresponding to sequential steps for preparing the medicament dispenser for use where the dispenser is shown absent its outer housing. Figure 4a shows a medicament dispenser comprising a housing 220 provided with a mouthpiece cover 230. As may be seen in Figure 4a, the mouthpiece cover 230 has an arm 234 provided with a mounting aperture 236 for mounting for interaction with a ratchet 246 of a complex gear mechanism 240. In use, the mouthpiece cover 230 is rotationally movable about an axis defined by the rotational axis of the ratchet 246.

In Figure 4a, the mouthpiece cover 230 is in a first position in which the mouthpiece is covered thereby. The housing 220 may be provided with a counter window (not shown) through which a dose count indicia of an electronic dose counter or a mechanical count wheel (not shown) may be viewed.

In Figure 4b, the mouthpiece cover 230 has been rotated to a second position, in which mouthpiece is part-uncovered, but in which the gear mechanism 240 and an associated dispensing mechanism, as described in more detail below, is not actuated whereby no medicament dose is made available for inhalation. Additionally, no actuation of the dose counter (not shown) has taken place whereby the count indicia stays the same.

In Figure 4c, the mouthpiece cover 230 has been rotated further to a third position to fully uncover or open the mouthpiece. Part of the cover 230 extends almost to the base 221 of the housing 220 in this position. As a result of the further movement from the second to third position the gear mechanism (described in more detail with reference to Figures 5 and 6a to 6c) and the dispensing mechanism (described in more detail above) have been actuated in the dispenser to make a medicament dose available for inhalation. In other words, the medicament dispenser is now primed for use. The movement has also resulted in actuation of the dose counter (mechanism not visible) of the

medicament dispenser so as to decrease or increase the dose count indicia by one unit.

After use, the mouthpiece cover 230 is returned to the first position (i.e. as in Figure 4a). This corresponds to the storage ('mouthpiece protected') position of the dispenser.

Figures 5a and 5b shows aspects of the gear mechanism 240 and of the internal dispensing mechanism of the medicament dispenser. Figure 5b shows the medicament dispenser having two medicament packs 200a, 200b in the form of strips. At the opening station 233, the cover sheet 212a, 212b and the base sheet 210a, 210b of each pack 200a, 200b are peelably separable about separators 236a, 236b. Rotatable base take-up spindle 213a, 213b anchors the end 214a, 214b of each respective base sheet 210a, 210b and progressive rotation of each respective base take-up spindle 213a, 213b results in the base sheet 210a, 210b being wound up therearound into a tight coil. The separated cover sheet 212a, 212b coils about respective cover take-up wheel 217a, 217b. Each cover take-up wheel 217a, 217b comprises a central hub, to which the ends 216a, 216b of the cover sheets 212a, 212b are respectively attached and about which it is wound up.

In Figure 5a, housing 220 may be seen to be provided with an internal chassis 228 for outward receipt of the parts of the gear mechanism 240. Within the chassis 228, there are provided mirror-image (left and right) dispensing mechanisms for dispensing medicament. The gear mechanism 240 can be considered to form part of the dispensing mechanisms. The gear mechanism 240 may be seen to comprise ratchet gear 242 mounted on drive spindle 231. The ratchet gear 242, like the other gears, is a wheel form having opposed inner and outer faces 241, 243 (relative to the exterior of the dispenser) and an outer circumferential surface 245a therebetween. The outer face 243 is recessed to define an inner circumferential surface 245b in opposed relation to the outer circumferential surface 245a. As will be seen, the outer and inner circumferential surfaces 245a, 245b are provided with a stepped profile to give

respective outer and inner ratchet features 244a, 244b for ratcheted interaction with a ratchet 246, which interaction will be described in more detail with reference to Figures 6a to 6c. The ratchet features 244a, 244b are equi-angularly spaced-apart ratchet teeth; in this embodiment there are five teeth on each circumferential surface 245a, 245b. The teeth 244a on the outer circumferential surface 245a (the 'outer teeth 244a') are offset from the teeth 244b on the inner circumferential surface 245b (the 'inner teeth 244b'). In other words, none of the inner teeth 244b lie on the same radius from the axis of rotation of the gear 242 as the outer teeth 244a.

As will be seen from Figures 5a and 6a, the inner circumferential surface 245b comprises surface segments 249 connecting each adjacent pair of inner teeth 244b. Each surface segment 249 consists of first and second sections 249a, 249b which extend inwardly from opposed ends of the segment 249, the first section 249a extending inwardly to the second section 249b from one inner tooth 244b and the second section 249b extending inwardly to the first section 249a from the next adjacent inner tooth 244b. The radius of curvature of the first section 249a is greater than the second section 249b whereby the second section 249b forms a ramp section with respect to the first section 249a.

Referring back to Figures 5a and 5b, it will be appreciated that the base take-up spindles 213a, 213b and the spindles (not shown) of the cover take-up wheels 217a, 217b are respectively connected to base take-up gears 262a, 262b and cover take-up gears 261a, 261b. The index wheels 260a, 260b are also provided with gears. The inner face 241 of the ratchet gear 242 is provided with drive gear teeth 247 for drive interaction (meshing) with (i) the gear of a first one of the index wheels 260a, and (ii) a first idler gear 264. The gear of the first index wheel 260a meshes with a first one of the cover take-up wheel gears 261a and the gear of the second index wheel 261b, which in turn meshes with the second cover take-up gear 261b. The first idler gear 264 meshes with a first one of the base take-up spindle gears 262b and a second idler gear 265, which in turn meshes with the second base take-up spindle gear 262a. This gear train

arrangement provides for indexing of the medicament packs 200a, 200b and winding on of the base and cover sheets 210a, 210b, 212a, 212b on movement of the mouthpiece cover 230 from its second position to its third position.

A suitable counter mechanism for use in the dispenser is provided in WO-A-2005/079727 (Glaxo Group Limited) which is incorporated herein by reference. The base take-up spindle 213a, 213b can be used to drive this counter mechanism by engagement with the drive wheel/step-up gear wheel thereof.

As shown in Figures 5a, 6a to 6c and 7, the ratchet 246 comprises a central hub 246a from the outer circumference of which depend a plurality of equi-angularly spaced-apart, circumferentially-oriented, resilient legs 246b. The ratchet hub 246a further comprises a boss 246c which, as shown in Figures 4a to 4c, fits in the mounting aperture 236 of the mouthpiece cover arm 234 for establishing a direct drive connection between the mouthpiece cover 230 and the ratchet 246 whereby rotary movement of the mouthpiece cover 230 between its first to third positions causes rotary movement of the ratchet 246 in the ratchet gear 242, as will be described in more detail shortly hereinafter. In this particular embodiment, five ratchet legs 246b depend from the ratchet hub 246a. In other words, the number of ratchet legs 246b is chosen to match the number of inner teeth 244b of the ratchet gear 242.

Interaction of the ratchet gear 242 with ratchet 246 may be better understood with reference to Figures 6a to 6c, which show movement of parts of the gear mechanism 240 of the medicament dispenser when prepared for use in sequential steps corresponding to those of Figures 4a to 4c.

In the rest position of Figure 6a (i.e. mouthpiece cover 230 closed), the ratchet 246 is angularly disposed in the ratchet gear 242 so that the inner teeth 244b of ratchet gear 242 are circumferentially spaced from the free ends of the ratchet legs 246b. In the second position of Figure 6b (i.e. mouthpiece cover 230 partially opened), the ratchet 246 has rotated round in the ratchet gear 242 to slide the ratchet legs 246b over the adjacent surface segments 249 of the inner circumferential surface 245b to engage the inner teeth 244b. It will therefore be

appreciated that in this second position, the ratchet gear 242 is ready for movement but has not yet been moved, and hence that the overall gear mechanism 240 and dispensing mechanisms have not been advanced. In the third position of Figure 6c (i.e. mouthpiece cover 230 fully opened), both the ratchet 246 and ratchet gear 242 rotate together (by 72° as shown) through inter-engagement of the ratchet legs 246b and the inner teeth 244b such as to advance the overall gear mechanism 240 and dispensing mechanisms such as to index and advance each medicament pack 200a, 230b to open a pocket of each and to thereby make the medicament powder contained in each opened pocket available at the opening station 233 for simultaneous inhalation by the patient through the manifold 250 and the opened mouthpiece 226.

Referring to Figure 7, the dispenser further comprises an internal retaining plate 281 for covering the gear mechanism 240. The retaining plate 281 is provided with an arcuate shelf 283 which lies over the ratchet gear 242 and the ratchet 246. One end of the shelf 283 is configured as a resilient finger 284 in which is provided a notch 285. The ratchet 246 includes a protrusion 246d which engages in the notch when the ratchet (and hence the mouthpiece cover 230) is in its first, rest position of Figure 6a, as shown in Figure 7. This inter-engagement of the ratchet protrusion 246d and the retaining plate notch 285 acts as a detent to hold the mouthpiece cover 230 in the 'mouthpiece closed' or rest position of Figures 4a and 6a.

The retaining plate 281 yet further comprises a fixed, resilient pawl leg 287 for interaction with the outer teeth 244a of the ratchet gear 246 to form an 'anti-return' feature for the ratchet gear 246. When the mouthpiece cover 230 is opened, to cause rotation of the ratchet 246 and then the ratchet gear 242 once the ratchet legs 246b engage the inner teeth 244b, the pawl leg 287 is not an impediment to the rotary movement of the ratchet gear 242 as the pawl leg 287 rides over the outer teeth 244a due to their orientation and the resilience of the pawl leg 287. However, when the mouthpiece cover 230 is returned to its closed position, in turn rotating the ratchet 246 to its rest position, the ratchet

gear 242 is held against return rotation by engagement of the pawl leg 287 with one of the outer teeth 244a. Accordingly, the reverse rotation of the ratchet 246 on closure of the mouthpiece cover 230 is not transmitted to the gear mechanism 240. Thus, on each occasion the mouthpiece cover 230 is fully opened and closed, the ratchet gear 242 is incremented in one rotary direction only.

When the mouthpiece cover 230 is returned to its first, covering position (Figure 4a) to rotate the ratchet 246 in the ratchet gear 242 back to its rest position (Figure 6a), the resilient legs 246b slide back over the inner circumferential surface 245b to be spaced behind different inner teeth 244b ready for next opening of the mouthpiece cover 230.

In Figure 6a there is shown an enlarged view of one of the gear teeth of index wheel 260a showing the profile thereof. The gear teeth of all of the gears in the gear mechanism are provided with this profile.

Different embodiments of the present invention will now be described in relation to the following Figures 8 to 20c. The reference numbers of similar components to the previous Figures have been incremented by 100, and the relevant description of those components above should be taken to apply.

Figure 8 shows a fault detector according to one embodiment of the present invention, which operates in a medicament dispenser device comprising a pair of the medicament packs, such as shown in Figure 1. In this particular embodiment, the fault detector is provided to the device of Figure 2, and like references denote like features.

The fault detector is designed to detect a condition in which medicament is potentially not being released. In particular, the fault detector is designed to detect fault conditions including tearing, breaking and delamination of at least one of the cover sheets 312a, 312b. As mentioned previously, each medicament pack 300a, 300b has a first structure, namely a base sheet 310a, 310b and a second structure, namely a cover sheet 312a, 312b, the cover sheet 312a, 312b being secured to the base sheet 310a, 310b. The cover sheet 312a, 312b has a laminated construction with an inner layer secured to the first structure and an

outer layer. The inner layer has a property which is different from that in the outer layer, the property being preferably a material comprised in the inner layer which is not comprised in the outer layer. The material is preferably a metallic layer so that the inner layer comprises at least a metallic layer and the outer layer comprises a non-metallic layer which is typically a paper layer.

Also as mentioned before, at the opening station 333, the cover sheet parts 312a, 312b and base sheet parts 310a, 310b of each strip 302a, 302b are peelably separable about a respective separator 336a, 336b. The separated cover sheet parts 312a, 312b and base sheet parts 310a, 310b are then advanced on respective first and second paths in the dispenser and are wound on respective cover take-up wheel 330a, 330b and base take-up spindle (not shown). If one of the cover sheets delaminates, parts of the cover sheet are not peeled off the base sheet so that only the paper layer of the cover sheet is separated from the base layer. Further dispensing of medicament from that strip may thus not be possible despite the strip continuing to be fed through the device, and the delaminated paper layer of the cover sheet being wound up on the cover take-up wheel 330a, 330b in response to user actuation of the dispenser.

If, on the other hand, the failure event is one of the cover sheets 312a, 312b tearing or breaking, then, upon continued user actuation of the dispenser, the cover sheet downstream of the tear/break will be wound up on the cover take-up wheel 330a, 330b whereas the cover sheet upstream of the tear/break will remain attached to the base sheet and be wound up with the base sheet on the base take-up spindle (not shown). In other words, the cover take-up wheel 330a, 330b will no longer wind-up any new cover sheet.

In the embodiment illustrated in Figure 8, the fault detector is an electronic fault detector which comprises two sensors 339a, 339b being located on one side of the second path associated with each separated cover sheet 312a, 312b and having input regions located adjacent to the second path associated with each separated cover sheet 312a, 312b. The sensors 339a, 339b may be

planar and silicon-based, and are electrically coupled to an electronic circuit (not shown) of the medicament dispenser.

The fault detector also comprises a radiation source 348 electrically coupled to the electronic circuit (not shown) of the medicament dispenser, the radiation source 348 being an electromagnetic radiation source, preferably a light source, such as a light-emitting diode (LED). In a preferred embodiment, the radiation source 348 is positioned to direct radiation into the manifold 350 between the multi-pocket index wheels 328a, 328b. The radiation source 348 preferably emits infra-red light at a wavelength of approximately 900 nm. The light is emitted in the manifold 350 which is preferably made of a plastics material, for instance high density polyethylene (HDPE), and which is located on the opposing side of the second path from the sensor 339a, 339b. The manifold 350 acts as a semi-transparent light guide, conveying the light from the radiation source 348 to a position adjacent each sensor 339a, 339b.

Each sensor 339a, 339b is located between each respective separator 336a, 336b and cover sheet driver (take-up spindle) 330a, 330b so that the separated cover sheets 312a, 312b are advanced adjacent to an input region of each sensor 339a, 339b, between the adjacent position where light from the radiation source 348 is conveyed and the sensor. The sensors 339a, 339b are capable of detecting an absence of at least a part of the cover sheets 312a, 312b, preferably the absence of the metallic layer, in the second paths of either of the separated cover sheets 312a, 312b based on an amount of radiated light passing through the separated cover sheets 312a, 312b and detected by the sensors 339a, 339b. In a normal operating mode, i.e. when a separated cover sheet 312a, 312b is not delaminated, the metallic layer of the separated cover sheet 312a, 312b is substantially opaque and does not transmit light from the adjacent position to the input region of the sensor 339a, 339b but instead blocks the light. Thus, the sensors 339a, 339b do not normally detect any significant amount of light from the radiation source 348 conveyed by the manifold, indicating that there is no fault.

In the case that a cover sheet delaminates, in which case the separated cover sheet 312a, 312b only comprises one or more non-metallic paper layers which are relatively light transmissive, the winding of the non-metallic layer(s) carries on but the sensor 339a, 339b detects a relatively high amount of light passing through the paper layer. The absence of metallic layer is thus detected in the separated cover sheet 312a, 312b. This is indicative that the metallic layer is still overlying the base sheet 310a, 310b, the medicament locations remaining enclosed in the base sheet, preventing release of the medicament powder in the unopened pockets of that strip for patient inhalation.

Likewise, if one of the strips tears or breaks, there will be no cover sheet interposed between the radiation source and the associated sensor 339a, 339b so that the sensor 339a, 339b detects a relatively high amount of light indicative of strip failure.

In an alternative arrangement to the one described in relation to Figure 8, the sensors 339a, 339b may be located on the manifold side of the second path and a radiation source 348 may be located on the opposing side of each second path from the sensors 339a, 339b.

The radiation source 348 and the sensors 339a, 339b are coupled by electrical wires (not shown) to an electronic circuit (not shown) of the medicament dispenser. One or more of the radiation source 348, the sensors 339a, 339b and components of the electronic circuit may be mounted on a printed circuit board (PCB) which is fitted inside the dispenser. The electronic circuit is adapted to produce an output signal indicating a fault condition based on the absence of metallic layer detected by either of the two sensors 339a, 339b. As will be described in some embodiments below, the output signal produced by the electronic circuit may be used to trigger an electrically-driven locking mechanism which provides a clear indication to the patient of such failure.

Light from the radiation source 348 is emitted in response to the medicament dispenser being operated by the user, e.g. through movement of a

trigger, for instance a mouthpiece cover, such as described with reference to Figures 3 to 7. In the latter case, light is emitted from the radiation source 348 as the mouthpiece cover is moved from the closed position (Figure 4a) to the fully opened position (Figure 4c) to advance strips for next patient use.

Ambient light may be a problem in that even if the sensors 339a, 339b do not detect any significant amount of light from the radiation source 348 (this would be the case when the dispenser operates normally), the sensors 339a, 339b may still detect a relatively high amount of ambient light entering the medicament dispenser which would indicate that medicament is not being released and that the dispenser does not operate normally. This would be the case where the radiation source 348 emits light in response to a mouthpiece cover being moved to open the mouthpiece, as ambient light may then enter the medicament dispenser.

In order to solve this particular problem, the light emitted by the radiation source 348 may be modulated in order to avoid interference due to ambient light but also due to residue of powder which may be deposited inside the dispenser such as on the surfaces of the radiation source 348, the manifold 350 and the sensor 339a, 339b. Modulation of the light emitted by the radiation source 348 is provided by a microcontroller of the electronic circuit shown in Figure 11. The microcontroller is capable of discriminating the modulated signal detected by the sensors from the ambient light signal detected by the sensors, and of subtracting the detected ambient light signal from the detected modulated signal. The resulting signal is then used to indicate whether the dispenser is in a fault condition or not.

As explained previously, the release of medicament from the open pockets (referenced 204a, 204b in Figure 2) of both the first 302a and second 302b strips is accessible via the manifold 350. To access the contents of the opened pockets, the patient breathes in through the mouthpiece (not shown) resulting in negative pressure being transmitted through the manifold 350 to the opened pockets of the strips 302a, 302b at the opening station 333. This

typically results in the creation of a venturi effect which results in the powder contained within each of the opened pockets being drawn out through the manifold 350 and thence to the mouthpiece as a combination medicament for inhalation by the patient. It be appreciated that, mixing of each separately delivered component of the combined medicament product happens as the powder is transported from each opened pocket to the mouthpiece.

Figure 9 is a cross-sectional side view of a manifold 450 showing its "in use" relationship with the medicament strips 402a, 402b of a medicament dispenser device and with a fault detector according to an embodiment of the present invention. In this particular embodiment, the arrangement is for the device of Figures 3 to 7 and thus the manifold 450 and strips 402a, 402b are those described for Figures 3 to 7. Similarly, the fault detector has close correspondence to the fault detector described with Figure 8. Accordingly, like reference numerals denote like features in the previous descriptions.

The fault detector is designed to detect a condition in which medicament is potentially not being released. In particular, the fault detector is designed to detect fault conditions including tearing, breaking and delamination of at least one of the cover sheets 412a, 412b, as described for Figure 8.

The fault detector is an electronic fault detector and comprises sensors 439a, 439b located on each side of the manifold 450 and a radiation source 448, in this instance an LED, positioned in proximity of the end of the manifold 450 which is opposite the mouthpiece end. The sensors 439a, 439b may be planar and silicon-based, and like the radiation source, are electrically coupled to an electronic circuit (not shown) of the medicament dispenser. In a preferred embodiment, the radiation source 448 is positioned to direct radiation into the manifold 450. The radiation source 448 preferably emits infra-red light at a wavelength of approximately 900 nm. The light is emitted in the manifold 450 which is preferably made of a plastics material, for instance high density polyethylene (HDPE), and which is located on the opposing side of the second path from the sensors 439a, 439b. The manifold 450 acts as a semi-transparent

light guide, conveying the light from the radiation source 448 to a position adjacent each sensor 439a, 439b.

When the mouthpiece cover (not shown) of the medicament dispenser is fully opened (see Figure 4c), the gear and dispensing mechanisms (not shown) of the dispenser are actuated to cause each blister strip 402a, 402b to be advanced and a single pocket 404a, 404b of each strip to be peeled open about a respective separator 436a, 436b. The separated cover sheet 412a, 412b and base sheet 410a, 410b are shown following different first and second paths. The separated cover sheet 412a, 412b is advanced on a second path between the manifold 450 and an input region of the sensor 439a, 439b, adjacent a position where the light from the radiation source 448 is conveyed by the manifold 450, and is wound around a cover sheet driver/take-up spindle (not shown).

The peeled-open blister pocket 404a, 404b of each strip 402a, 402b lies adjacent a respective one of the pairs of chimney exits 454a, 454b and chamber inlets (not shown) of the manifold 450.

Specifically, the open blister pocket 404a of the first blister strip 402a locates adjacent the first chimney exit 454a and the first chamber inlet (not shown) and the open blister pocket 404b of the second blister strip 402b likewise locates adjacent the other chimney exit 454b and the second chamber inlet (not shown). As described previously with reference to Figure 1, the blister pockets 404a, 404b are elongate, extending sideways relative to the longitudinal axis of the strip 402a, 402b. The pockets 404a, 404b can therefore be considered to have first and second sides on opposing sides of the strip longitudinal axis. When the open pockets 404a, 404b are presented to the manifold 450 at the opening station, the pockets 404a, 404b are oriented so that the sideways orientation thereof is aligned to the direction between the respective chimney exits 454a, 454b and chamber inlets. Thus, the chimney exits 454a, 454b and the chamber inlets lie over the different sides of the pockets 404a, 404b, whereby, in use, the air flows through the pockets 404a,

404b in the sideways orientation thereof; i.e. sideways relative to the longitudinal axis (or length direction) of the strip 402a, 402b.

When a patient inhales at the mouthpiece, an airstream (referenced 283 in Figure 3) flows from outside of the dispenser device into the manifold 450 solely through the air inlet grille (referenced 270 in Figure 3) into the chimney 452 via the chimney inlet 453, which is in juxtaposed relation with the air inlet grille 270. First (or primary) portions of this airstream flow into the opened blister pocket 404a, 404b of each strip 400a, 400b at the opening station via the respective chimney exits 454a, 454b, thereby entraining the medicament powder contained in the pockets in the airstream, and thence out of the pockets 404a, 404b into the chamber (referenced 260 in Figure 3) via chamber inlets. The airstream with entrained medicament powder then flows out of the mouthpiece (referenced 226 in Figure 3) into the patient's respiratory tract.

A single D-shaped bleed hole 480 is provided to the wall 459 which separates the chimney 452 from the chamber 260. The D-shaped bleed hole 480 locates adjacent to both the chimney exits 454a, 454b and the chamber inlets (referenced 273a, 273b in Figure 3). In use, the bleed hole 480 acts such as to direct a second portion of the airstream 283 (the "bleed portion") from the chimney 452 directly into the chamber 260 to disruptively impact the first portions of the airstream 283 that transport the entrained medicament powder into the chamber 260 and thereby break up any powder agglomerate components thereof.

The sensors 439a, 439b are capable of detecting an absence of at least a part of the cover sheets 412a, 412b, preferably the absence of the metallic layer, in the second paths of either of the separated cover sheets 412a, 412b based on an amount of radiated light passing through the separated cover sheets 412a, 412b and detected by the sensors 439a, 439b. In a normal operating mode, i.e. when a separated cover sheet 412a, 412b is not delaminated, the metallic layer of the separated cover sheet 412a, 412b is substantially opaque and does not transmit light from the adjacent position to the input region of the sensor 439a,

439b but instead blocks the light. Thus, the sensors 439a, 439b do not normally detect any significant amount of light from the radiation source 448 conveyed by the manifold, indicating that there is no fault.

In the case that a cover sheet delaminates, in which case the separated cover sheet 412a, 412b only comprises one or more non-metallic (e.g. paper) layers which are relatively light transmissive, the winding of the non-metallic layer(s) carries on but the sensor 439a, 439b detects a relatively high amount of light passing through the paper layer. The absence of metallic layer is thus detected in the separated cover sheet 412a, 412b. This is indicative that the metallic layer is still overlying the base sheet 410a, 410b, the medicament locations remaining enclosed in the base sheet, preventing release of the medicament powder in the unopened pockets of that strip for patient inhalation.

Likewise, if one of the strips tears or breaks, there will be no cover sheet interposed between the radiation source and the associated sensor 439a, 439b so that the sensor 439a, 439b detects a relatively high amount of light indicative of strip failure.

Light from the radiation source 348 is emitted in response to the mouthpiece cover being moved from the closed position (Figure 4a) to the fully opened position (Figure 4c) to advance strips for next patient use.

Ambient light may be a problem as ambient light may enter the medicament dispenser on opening the mouthpiece cover. In order to solve this particular problem, the light emitted by the radiation source 448 may be modulated in order to avoid interference due to ambient light, and also due to residue of powder which may be deposited inside the dispenser such as on the surfaces of the radiation source 448, the manifold 450 and the sensor 439a, 439b. Modulation of the light emitted by the radiation source 448 is provided by a microcontroller of the electronic circuit to be described hereinafter with reference to Figure 11. The microcontroller is capable of discriminating the modulated signal detected by the sensors from the ambient light signal detected by the sensors, and of subtracting the detected ambient light signal from the

detected modulated signal. The resulting signal is then used to indicate whether the dispenser is in a fault condition or not.

In an alternative arrangement to the one described in relation to Figure 9, the sensors 439a, 439b may be located on the manifold side of the second path and a radiation source 448 may be located on the opposing side of each second path from the sensors 439a, 439b.

One or more of the radiation source 448, the sensors 439a, 439b and components of the electronic circuit may be mounted on a printed circuit board (PCB) which is fitted inside the dispenser. The electronic circuit is adapted to produce an output signal indicating a fault condition based on the absence of metallic layer detected by either of the two sensors 439a, 439b. As will be described in some embodiments below, the output signal produced by the electronic circuit may be used to trigger an electrically-driven locking mechanism which provides a clear indication to the patient of such failure.

The medicament dispenser of the present invention may in an alternate embodiment be designed to receive a single elongate medicament pack 100. The fault detector may in that case comprise a radiation source, in this instance an LED, being located adjacent a second path on one side of the separated cover sheet and a single sensor being located on the other side of the same separated cover sheet. In this alternate embodiment, the sensor is also capable of detecting an absence of metallic layer in the separated cover sheet based on an amount of radiated light passing through the separated cover sheet and detected by the sensor. Likewise, if there is an absence of a cover sheet *per se*, due to it tearing or breaking, the light passes unimpeded to the sensor for detection of this failure.

Figure 10 is a schematic diagram showing an electronic circuit and components of a medicament dispenser device according to one embodiment of the present invention. In this embodiment, the medicament dispenser is designed to receive two medicament packs, such as shown in Figure 1. More particularly, in this embodiment the circuit of Figure 10 is described for use in

the fault detectors of the medicament dispensers of Figures 2 and 8 or Figures 3 to 7 and 9, respectively, with like reference numerals again being used for like features.

In Figure 10, the electronic circuit comprises a fault detector, including a radiation source 548, in this instance an LED, and a first sensor 539a associated with a first separated cover sheet 512a. The circuit also comprises a number of resistors 568a-568e and Schottky diodes 568f-568g. A sub-circuit B identical to sub-circuit A is represented and comprises a second sensor (not shown) associated with the second separated cover sheet (not shown) which is capable of detecting a signal from the radiation source 548.

The electronic circuit is powered by a power source 563 by the closure of the switch 569 when the medicament dispenser is operated, in particular when full rotation of the mouthpiece cover has occurred (as shown in Figure 4c). The switch 569 may be momentarily closed when the mouthpiece cover is moved from a closed position to a fully opened position (as described with reference to Figures 20a to 20c). Alternatively, the switch may be closed when the mouthpiece cover is in a fully opened position. In this case, activation of the switch 569 when the mouthpiece cover is left open is preferably disabled after a predetermined amount of time in order to save battery power. The power source 563 is in this embodiment a battery but any other energy source may be used instead.

The electronic circuit is adapted to produce an output signal indicating a fault condition based on the absence of metallic layer detected by the first sensor 539a or the second sensor of sub-circuit B. The signal detected by any of the sensors (e.g. sensor 539a) is amplified by an operational amplifier 566 in order to drive a field-effect transistor which acts as a switch 567 which in turn drives a visual fault indicator 562. The fault indicator 562 is in this embodiment a light source, for example an LED, which lights up for indicating to a user of the dispenser when a fault has been detected by the fault detector. The fault indicator may also comprise a tactile indicator and/or audible indicator. A

separated cover sheet 512a is also shown to illustrate the fact that it is located between the radiation source 548 and the sensor 539a. The second separated cover sheet (not shown) is also located between the radiation source 548 and the second sensor of sub-circuit B.

In this embodiment, the medicament dispenser is provided with a visual fault indicator in the form of a LED 562. Alternatively, or in addition, the medicament dispenser is further provided with a locking mechanism, such as to be described with reference to Figures 12 to 19.

Figure 11 is a schematic diagram showing an electronic circuit and components of a medicament dispenser device according to a further embodiment of the present invention. In this embodiment, the medicament dispenser is designed to receive two medicament packs, such as shown in Figure 1. More particularly, in this embodiment the circuit of Figure 11 is described for use in the fault detectors of the medicament dispensers of Figures 2 and 8 or Figures 3 to 7 and 9, respectively, with like reference numerals again being used for like features.

In this embodiment, the fault detector comprises a radiation source 648, in this instance an LED, and two sensors, associated with each separated cover sheet. A first sensor 639a in sub-circuit A is associated with a first separated cover sheet 612a. A second sensor (not shown) in sub-circuit B which is identical to sub-circuit A is associated with a second separated cover sheet (not shown). The output signal of the electronic circuit is used to trigger one of the locking mechanisms 692 described in relation to Figures 12 to 19 hereinafter. Even though the medicament dispenser device is designed to receive two medicaments packs 100 in the form of elongate strips, there is preferably only one locking mechanism 692 per dispenser which is driven on the basis of the signal detected by each of the sensors of sub-circuits A and B as follows.

The signal detected by each sensor (e.g. 639a) is amplified by an operational amplifier 666 and fed to a microcontroller 671. The microcontroller 671 drives a field-effect transistor which acts as a switch 667 which in turn

drives the locking mechanism 692. The driving of the locking mechanism 692 is typically possible using only a 3V battery source 663 at 180 mA. A ceramic capacitor 665 may be used across the battery 663 to boost the current delivered by the battery when the switch 669 is closed. A Schottky diode 672 and electrolytic capacitor 673 prevent the voltage supplied to the microcontroller 671 from dipping when the locking mechanism places a high current demand from the battery 663. The microcontroller 671 may be used to modulate the light signal emitted by the radiation source 648, in this instance an LED, as explained above.

The electrical components of the electronic circuit and the circuitry interconnecting the different components, described in relation to the embodiments of Figures 10 and 11, are preferably mounted on a PCB which is typically fitted between the shell cover parts of the dispenser. The PCB may also include the radiation source and possibly the sensors (although not in this embodiment) and the fault indicator light so that when the PCB is fitted between the shell cover parts of the dispenser, the radiation source, in this instance an LED, is located in the proximity of the narrow end of the manifold and the sensors are located between the sides of the manifold and the cover sheet drivers. The fault indicator light may extend through an opening, or may be viewable through a transparent window provided, in one of the shell cover parts so as to be clearly visible to a user of the dispenser.

Figures 12 to 19 are schematic diagrams of locking mechanism for a medicament dispenser device in accordance with different embodiments of the present invention. In each of these embodiments, the locking mechanism is arranged to prevent further use of the medicament dispenser by locking with an element of the dispenser, in the event that a fault, such as but not exclusively delamination, is detected by the fault detector. Each of these locking mechanisms comprises an actuator which is designed to maintain the locking mechanism in a non-locking position and to release the locking mechanism in a locking position in the event that a fault has been detected.

The locking mechanisms of Figures 12 to 19 are hereinafter described with reference to inclusion in the medicament dispensers of Figure 2 or Figure 3, with like reference numbers designating like features. Moreover, the locking mechanisms of Figures 12 to 19 are described in relation to being electrically coupled to the electronic circuit of Figure 11 and being adapted to move to the locking position in response to the electronic circuit producing an output signal representing detection by the fault detector of a condition indicating that medicament is not being released. However, it will be appreciated that the locking mechanisms of the invention may be operated in response to other fault detectors, e.g. other non-mechanical fault detectors or mechanical fault detectors.

A first embodiment of a locking mechanism is shown schematically in Figures 12a to 13b, Figures 13a and 13b being schematic side views in the direction of the arrows A of respective Figures 12a and 12b.

In this embodiment, the locking mechanism 792 includes a locking element in the form of a pin 790 and a biasing member in the form of a spring 711 which is located in a cavity of a cover sheet take-up spindle 730a. The cover sheet take-up spindle 730a is fixed to an internal chassis 725 of the dispenser. The locking mechanism 792 also includes an actuator which is electrically coupled to the electronic circuit. The actuator comprises a wire segment 713 which is made of a shape memory alloy (SMA), which alloy is also known in the art as a "memory metal". A suitable SMA is Flexinol™ which is made of nickel–titanium alloy (nitinol). The wire segment 713 is held in tension between two axles 715a and 715b which are fixed to the chassis 725.

Each end of the wire segment is electrically coupled to the electronic circuit of the medicament dispenser using electrical wires (not shown) for instance. The actuator comprises a plate 727 rotatable around a pivot 729, the pivot 729 being fixed to the chassis 725. A semi-circular actuating element 733 is rotatably mounted on the plate 727 by way of a pivot 735 which is fixedly mounted to the plate 727. The wire segment 713 passes inside a groove (not

shown) which is located along the edge of the semi-circular part of the actuating element 733. A resilient member 737 (e.g. a spring) connects the pivot 735 to an axle 755 which is fixed to the chassis 725.

In a normal operating mode (Figures 12a and 13a), the pin 790 and spring 711 are kept in a retracted position inside the cover sheet driver 730a by the plate 727. When a fault is detected by the fault detector of the medicament dispenser, the wire 713 is driven electrically by the electronic circuit of the medicament dispenser and contracts. In response to the contraction of the wire 713 which is held in tension between the two fixed axles 715a and 715b, the semi-circular actuating element 733, which is retained by spring 737, rotates around the pivot 735 and is pulled by the wire 713 towards the axles 715a, 715b. Movement of the semi-circular actuating element 733 triggers the plate 727 to rotate around the pivot 729, thus releasing the pin 790 which then projects out of the cavity (as shown in Figure 13b) under the action of the spring 711, visually indicating the fault.

As an alternative, in the normal operating mode, the plate 727 may engage in a slot in the pin 790, instead of overlying the pin 790, in order to keep the pin 790 in a retracted position inside the cover sheet driver 730a.

In this first embodiment and in the following embodiments of the locking mechanism, the pin 790 projects through an opening in the shell cover part 720a in the fault indicating position. The pin 790 preferably locks with an element of the medicament dispenser., Preferably the pin 790 engages the mouthpiece cover (e.g. cover 230, Figure 4a) as it returns to its closed position and stops the mouthpiece cover being opened again, so that further use of the dispenser is prohibited. By blocking the mouthpiece cover in its closed position, the pin 790 provides a tactile indication of a fault to a user. The patient is thereby given a clear message that the medicament dispenser has failed and that a replacement must be obtained. As an alternative, when projecting out of the cavity of the cover sheet driver, the pin 790 does not allow the mouthpiece cover to return from a third position (shown in Figure 4c) to a first position (shown in

Figure 4a) after actuation of the dispensing mechanism. Instead, the mouthpiece cover is blocked in an intermediate position. As a result, the patient is thereby given a clear message that the medicament dispenser has failed. Also, further actuation of the dispensing mechanism, which can only be triggered by the patient moving the mouthpiece cover from the first position to the third position, is inhibited.

As mentioned in relation to Figure 11, only one locking mechanism is needed per medicament dispenser even though the medicament dispenser device is designed to receive two medicaments packs 100 in the form of elongate strips. The locking mechanism is driven on the basis of the signal detected by each of the sensors.

A further embodiment of the locking mechanism is shown schematically in Figures 14a to 15b. Figures 15a and 15b are schematic side views in the direction of the arrows B of respective Figures 14a and 14b.

The locking mechanism 892 in this embodiment comprises a pin 890 and spring 811 similar to that described above, and an actuator. The actuator comprises a lever 827 which holds the pin and spring inside a cavity of the cover sheet driver 830a. The actuator comprises a DC electrical motor 889 electrically coupled to the electronic circuit of the medicament dispenser. The DC motor 889 comprises a stator 891 and a rotor 893 which drives in rotation a drive shaft 879 on which a pinion wheel 894 is fixedly mounted. The actuator also comprises a gearbox which may include at least two, preferably at least three, toothed gearwheels 857, 875, 877.

Each gearwheel 857, 875, 877 comprises a shaft which is fixed to the chassis 825 and at least one wheel, each wheel having a number of teeth around its circumference. The wheels 895, 896 are mechanically coupled and are mounted in rotation on the shaft of the gearwheel 877. The wheels 897, 898 are mechanically coupled and are mounted in rotation on the shaft of the gearwheel 875. The wheel 899 is mounted in rotation on the shaft of the gearwheel 857 and is mechanically coupled to the lever 827. Pinion wheel 894 meshes with

wheel 895, wheel 896 meshing with wheel 897 and wheel 898 meshing with wheel 899. The wheels are preferably of different diameters and are chosen so that the torque of the gearwheel 857 is sufficient to rotate the lever 827.

When driven electrically by the electronic circuit in the case that a fault has been detected by the fault detector described above, the DC motor drives the pinion 894 which rotates the wheel 895 around the shaft of the gearwheel 877. The wheel 896 which is mechanically coupled to wheel 895 in turn rotates the wheel 897 around the shaft of the gearwheel 875. Then, the wheel 898 which is mechanically coupled to wheel 897 rotates the wheel 899 and the lever 827 around the shaft of the gearwheel 857 (as shown in Figures 14b and 15b), thus releasing the pin 890 which under the action of the spring 811 then projects out of the cavity to lock a feature of the operating mechanism of the dispenser, for instance the mouthpiece cover (not shown) as described previously.

A further embodiment of the locking mechanism is shown in Figures 16a to 17b, Figures 17a and 17b being sectional views of respective Figures 16a and 16b along the lines C-C.

The locking mechanism 992 in this embodiment comprises a pin 990 and spring 911 similar to that described above and an actuator. The actuator comprises a solenoid actuator 901 which includes a circular coil 903 electrically coupled to the electronic circuit of the medicament dispenser and an axle 907 which is fixed to the housing of the solenoid actuator 901. An armature 905 on which a stem 927 is fixedly mounted is mounted in a sliding fashion on the axle 907. A spring 909 is fitted around the axle 907 and connects the housing of the solenoid actuator 901 to the armature 905. When the coil 903 is not electrically driven (Figures 16a and 17a), the spring 909 forces the armature 905 away from the coil 903, the stem 927 holding the pin 990 and spring 911 inside a cavity of the cover sheet driver 930a.

When electrically driven in the case that a fault has been detected by the fault detector described above, the coil 903 of the solenoid actuator 901 is activated and the armature 905 and stem 927 slide on the axle 907 moving

towards the coil 903. The stem 927 thus releases the pin 990 which then projects out of the cavity under the action of the spring 911 (as shown in Figures 16b and 17b) to lock a feature of the operating mechanism of the dispenser, for instance the mouthpiece cover (not shown) as described previously.

A further embodiment of the locking mechanism is shown in Figures 18a to 19b. Figures 19a and 19b are schematic side views as indicated by the arrows D of respective Figures 18a and 18b. The locking mechanism 1092 in this embodiment comprises a pin 1090 and spring 1011 similar to that described above, a lever 1027 which holds the pin 1090 inside a cavity of the cover sheet driver 1030a and an actuator which is mechanically connected to the lever. The actuator comprises a servo motor which includes a DC electric motor 1089 which is electrically connected to the electronic circuit of the medicament dispenser. The servo motor also comprises a gearwheel 1077 having a shaft fixed to the chassis 1025. The motor comprises a stator 1091 and a rotor 1093 to which a shaft 1079 is fixedly connected. A pinion wheel 1094 fixedly mounted on the shaft 1079 meshes with a wheel 1095 of a gearwheel 1077. The wheel 1095 and the lever 1027 are mechanically connected and mounted in rotation on the fixed shaft of the gearwheel 107.

The angular position of the lever 1027 is controlled by a pulse width modulation (PWM) signal, as well known in the art, which is provided by the microcontroller 671 of the electronic circuit shown in Figure 11. The lever 1027 moves to an angular position which is linearly proportional to the width of the pulse. The servo motor also includes a position sensor (not shown) to determine the angular position of the lever 1027, the position sensor being electrically connected to the microcontroller 671.

When driven by the electronic circuit in the case that a fault has been detected by the fault detector described above, the rotor 1093 rotates driving the pinion wheel 1094 which in turn drives the gearwheel 1095. The lever 1027 being connected to the gearwheel 1095, the lever rotates (as shown in Figure 18b), thus releasing the pin 1090 which then projects out of the cavity of the

cover sheet driver 1030a, to lock a feature of the operating mechanism of the dispenser, e.g. the mouthpiece cover (not shown) as described previously.

Referring to Figures 20a to 20c, there is shown a schematic view of one embodiment of an arrangement for activating the electronic circuit of the medicament dispenser of the present invention. This embodiment is described with particular reference to the activation of the electronic circuit of Figures 10 and Figure 11 as used in the dispenser of Figures 3-7 and 9. In this embodiment, the switch 1169 of the circuit is shown having an actuating arm 1172 and two electric terminals 1172a, 1172b, the arm 1172 being rotatable around the terminal 1172a. The switch 1169 is in this embodiment mounted on the retaining plate 281 of Figure 7. Electrical wires (not shown) couple the two electric terminals 1172a, 1172b to the electronic circuit of the medicament dispenser. The actuating arm 1172 of the switch 1169 interacts with the resilient pawl leg 1187 which interacts with the outer teeth 1144a of the ratchet gear 246 as described in relation to Figure 7. When the mouthpiece cover 230 is opened, an outer tooth 1144a of the ratchet gear 246 is rotated in an anti-clockwise direction and engages with a pawl leg 1187. Figure 20a shows the position of the switch 1169, pawl leg 1187 and outer teeth 1144a when the mouthpiece cover is in a closed position. When the mouthpiece cover is moved from a closed position (Figure 20a) to a fully opened position (Figure 20c), the pawl leg 1187 briefly moves in contact with the actuating arm 1172 of the switch 1169, thus momentarily closing the switch 1169 as shown in Figure 20b. Once the mouthpiece cover 230 is in a fully open position, the pawl leg 1187 moves back to its initial position and the switch 1169 is opened again (Figure 20c). If a locking mechanism is triggered by the electronic circuit, such as in the circuit of Figure 11, in this embodiment the locking mechanism does not lockingly engage the mouthpiece cover (230, Figures 4a-c) until the mouthpiece cover 230 returns to the closed position (Figure 4a).

In the above-described embodiments, the manifold is a one-piece, injection moulded plastic component. More particularly, the manifold is

preferably made from high density polyethylene (HDPE), since this material is suitable for injection moulding the manifold, in particular high-speed injection moulding, while having a sufficiently low surface energy to minimise or inhibit deposition of the medicament powder thereon. However, other materials and manufacturing or moulding processes could be used. As other possible materials there may be mentioned fluoropolymers, for instance fluorinated ethylene-propylene (FEP), and other non-fluoropolymers, for instance polypropylene (PP).

It may be appreciated that any of the parts of the device or any component thereof which contacts medicament may be comprised of or coated with materials such as fluoropolymer materials (e.g. PTFE or FEP) that reduce the tendency of medicament to adhere thereto. Any movable parts may also have coatings applied thereto which enhance their desired movement characteristics. Frictional coatings may therefore be applied to enhance frictional contact and lubricants (e.g. silicone oil) used to reduce frictional contact as necessary.

In particular, the manifold itself may be wholly or partly comprised of or alternatively coated partially or wholly with materials that reduce the tendency of medicament to adhere thereto. Such materials may for example, lower the surface energy of the relevant manifold surface. Suitably, fluoropolymer materials are employed. High density polyethylene (HDPE) and/or modified acetal materials are also suitable.

Suitable fluoropolymer materials include those comprising multiples of one or more of the following monomeric units: tetrafluoroethylene (PTFE), fluorinated ethylene propylene (FEP), perfluoroalkoxyalkane (PFA), ethylene tetrafluoroethylene (ETFE), vinyldienefluoride (PVDF), and chlorinated ethylene tetrafluoroethylene. Fluorinated polymers, which have a relatively high ratio of fluorine to carbon, such as perfluorocarbon polymers, e.g., PTFE, PFA and FEP are particularly suitable. Particularly when used as a coating, the fluoropolymer is optionally blended with a non-fluorinated polymer such as

polyamides, polyimides, polyamide imides, polyethersulfones, polyphenylene sulfides, and amine-formaldehyde thermosetting resins. These added polymers often improve adhesion of the polymer coating to the substrate. Preferred polymer blends are PTFE/FEP/polyamideimide, PTFE/polyether sulphone (PES) and FEP-benzoguanamine.

The medicament dispenser device herein is suitable for dispensing powdered medicament formulations, particularly for the treatment of respiratory disorders such as asthma and chronic obstructive pulmonary disease (COPD), bronchitis and chest infections.

In particular, the medicament dispenser device may be used in delivery of a medicament powder formulation based on one or more of the medicaments listed hereinbelow. Where the medicament dispenser device is to be used with just a single blister pack, the medicament formulation in that pack may comprise just one of the listed medicaments (a monotherapy) or a plurality of the listed medicaments (combination therapy). Where the medicament dispenser device is for use with plural (in particular two) blister packs, each pack may contain a medicament powder formulation comprising one or more of the listed medicaments, one pack containing at least one medicament not found in the, or at least one of the other packs. Where the medicament dispenser device is for use with two blister packs, the medicament powder formulation in one pack comprises a medicament not found in the other pack. Typically, each pack will have different medicament(s) than the other pack.

Appropriate medicaments may thus be selected from, for example, analgesics, e.g., codeine, dihydromorphine, ergotamine, fentanyl or morphine; anginal preparations, e.g., diltiazem; antiallergics, e.g., cromoglycate (e.g. as the sodium salt), ketotifen or nedocromil (e.g. as the sodium salt); antiinfectives e.g., cephalosporins, penicillins, streptomycin, sulphonamides, tetracyclines and pentamidine; antihistamines, e.g., methapyrilene; anti- inflammatories, e.g., beclomethasone (e.g. as the dipropionate ester), fluticasone (e.g. as the propionate ester), flunisolide, budesonide, rofleponide, mometasone e.g. as the

furoate ester), ciclesonide, triamcinolone (e.g. as the acetonide) or 6α, 9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxy-androsta-1,4-diene-17β-carbothioic acid S-(2-oxo-tetrahydro-furan-3-yl) ester; antitussives, e.g., noscapine; bronchodilators, e.g., albuterol (e.g. as free base or sulphate), salmeterol (e.g. as xinafoate), ephedrine, adrenaline, fenoterol (e.g. as hydrobromide), salmefamol, carbuterol, mabuterol, etanterol, naminterol, clenbuterol, flerbuterol, bambuterol, indacaterol, formoterol (e.g. as fumarate), isoprenaline, metaproterenol, phenylephrine, phenylpropanolamine, pirbuterol (e.g. as acetate), reproterol (e.g. as hydrochloride), rimiterol, terbutaline (e.g. as sulphate), isoetharine, tulobuterol or 4-hydroxy-7-[2-[[2-[[3-(2-phenylethoxy)propyl]sulfonyl]ethyl]amino]ethyl-2(3H)-benzothiazolone; adenosine 2a agonists, e.g. 2R,3R,4S,5R)-2-[6-Amino-2-(1S-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-5-(2-ethyl-2H-tetrazol-5-yl)-tetrahydro-furan-3,4-diol (e.g. as maleate); α_4 integrin inhibitors e.g. (2S)-3-[4-({[4-(aminocarbonyl)-1-piperidinyl]carbonyl}oxy)phenyl]-2-[((2S)-4-methyl-2-{[2-(2-methylphenoxy) acetyl]amino}pentanoyl)amino] propanoic acid (e.g. as free acid or potassium salt), diuretics, e.g., amiloride; anticholinergics, e.g., ipratropium (e.g. as bromide), tiotropium, atropine or oxitropium; hormones, e.g., cortisone, hydrocortisone or prednisolone; xanthines, e.g., aminophylline, choline theophyllinate, lysine theophyllinate or theophylline; therapeutic proteins and peptides, e.g., insulin or glucagon; vaccines, diagnostics, and gene therapies. It will be clear to a person skilled in the art that, where appropriate, the medicaments may be used in the form of salts, (e.g., as alkali metal or amine salts or as acid addition salts) or as esters (e.g., lower alkyl esters) or as solvates (e.g., hydrates) to optimise the activity and/or stability of the medicament.

The formulated medicament product may in aspects, be a mono-therapy (i.e. single active medicament containing) product or it may be a combination therapy (i.e. plural active medicaments containing) product.

Preferred medicaments are selected from albuterol, salmeterol, fluticasone propionate and beclomethasone dipropionate and salts or solvates thereof, e.g., the sulphate of albuterol and the xinafoate of salmeterol.

Medicaments can also be delivered in combinations. Preferred formulations containing combinations of active ingredients contain salbutamol (e.g., as the free base or the sulphate salt) or salmeterol (e.g., as the xinafoate salt) or formoterol (eg as the fumarate salt) in combination with an anti-inflammatory steroid such as a beclomethasone ester (e.g., the dipropionate) or a fluticasone ester (e.g., the propionate) or budesonide. A particularly preferred combination is a combination of fluticasone propionate and salmeterol, or a salt thereof (particularly the xinafoate salt). A further combination of particular interest is budesonide and formoterol (e.g. as the fumarate salt).

Suitable medicaments or medicament components of a combination therapy product are typically selected from the group consisting of anti-inflammatory agents (for example a corticosteroid or an NSAID), anticholinergic agents (for example, an M_1, M_2, M_1/M_2 or M_3 receptor antagonist), other β_2-adrenoreceptor agonists, antiinfective agents (e.g. an antibiotic or an antiviral), and antihistamines. All suitable combinations are envisaged.

Suitable anti-inflammatory agents include corticosteroids and NSAIDs. Suitable corticosteroids which may be used in combination with the compounds of the invention are those oral and inhaled corticosteroids and their pro-drugs which have anti-inflammatory activity. Examples include methyl prednisolone, prednisolone, dexamethasone, fluticasone propionate, 6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester, 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxy- androsta-1,4-diene-17β-carbothioic acid *S*-(2-oxo-tetrahydro-furan-3S-yl) ester, beclomethasone esters (e.g. the 17-propionate ester or the 17,21-dipropionate ester), budesonide, flunisolide, mometasone esters (e.g. the furoate ester), triamcinolone acetonide, rofleponide, ciclesonide,

butixocort propionate, RPR-106541, and ST-126. Preferred corticosteroids include fluticasone propionate, 6α,9α-difluoro-11β-hydroxy-16α-methyl-17α-[(4-methyl-1,3-thiazole-5-carbonyl)oxy]-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester, 6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester, 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-(2,2,3,3-tetramethycyclopropylcarbonyl)oxy-androsta-1,4-diene-17β-carbothioic acid *S*-cyanomethyl ester, 6α,9α-difluoro-11β-hydroxy-16α-methyl-17α-(1-methycyclopropylcarbonyl)oxy-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester and 9α, 21 dichloro-11β, 17α methyl-1,4 pregnadiene 3, 20 dione-17-[2'] furoate (mometasone furoate).

Further corticosteroids are described in WO02/088167, WO02/100879, WO02/12265, WO02/12266, WO05/005451, WO05/005452, WO06/072599 and WO06/072600.

Non-steroidal compounds having glucocorticoid agonism that may possess selectivity for transrepression over transactivation and that may be useful in combination therapy through the manifold herein are disclosed WO03/082827, WO98/54159, WO04/005229, WO04/009017, WO04/018429, WO03/104195, WO03/082787, WO03/082280, WO03/059899, WO03/101932, WO02/02565, WO01/16128, WO00/66590, WO03/086294, WO04/026248, WO03/061651, WO03/08277, WO06/000401, WO06/000398 and WO06/015870.

Suitable NSAIDs include sodium cromoglycate, nedocromil sodium, phosphodiesterase (PDE) inhibitors (e.g. theophylline, PDE4 inhibitors or mixed PDE3/PDE4 inhibitors), leukotriene antagonists, inhibitors of leukotriene synthesis, iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine receptor agonists or antagonists (e.g. adenosine 2a agonists), cytokine antagonists (e.g. chemokine antagonists), inhibitors of cytokine synthesis or 5-lipoxygenase inhibitors. Examples of iNOS inhibitors include those disclosed in WO93/13055, WO98/30537, WO02/50021,

WO95/34534 and WO99/62875. Examples of CCR3 inhibitors include those disclosed in WO02/26722.

Suitable bronchodilators are β_2-adrenoreceptor agonists, including salmeterol (which may be a racemate or a single enantiomer, such as the *R*-enantiomer), for instance salmeterol xinafoate, salbutamol (which may be a racemate or a single enantiomer, such as the *R*-enantiomer), for instance salbutamol sulphate or as the free base, formoterol (which may be a racemate or a single diastereomer, such as the *R,R*-diastereomer), for instance formoterol fumarate or terbutaline and salts thereof. Other suitable β_2-adrenoreceptor agonists are 3-(4-{[6-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl] oxy} butyl) benzenesulfonamide, 3-(3-{[7-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-hydroxymethyl) phenyl] ethyl}-amino) heptyl] oxy} propyl) benzenesulfonamide, 4-{(1*R*)-2-[(6-{2-[(2, 6-dichlorobenzyl) oxy] ethoxy} hexyl) amino]-1-hydroxyethyl}-2-(hydroxymethyl) phenol, 4-{(1*R*)-2-[(6-{4-[3-(cyclopentylsulfonyl)phenyl]butoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl) phenol, N-[2-hydroxyl-5-[(1*R*)-1-hydroxy-2-[[2-4-[[(2R)-2-hydroxy-2-phenylethyl]amino]phenyl]ethyl]amino]ethyl]phenyl]formamide, and N-2{2-[4-(3-phenyl-4-methoxyphenyl)aminophenyl]ethyl}-2-hydroxy-2-(8-hydroxy-2(1*H*)-quinolinon-5-yl)ethylamine, and 5-[(*R*)-2-(2-{4-[4-(2-amino-2-methyl-propoxy)-phenylamino]-phenyl}-ethylamino)-1-hydroxy-ethyl]-8-hydroxy-1H-quinolin-2-one. Preferably, the β_2-adrenoreceptor agonist is a long acting β_2-adrenoreceptor agonist (LABA), for example a compound which provides effective bronchodilation for about 12 hours or longer.

Other β_2-adrenoreceptor agonists include those described in WO 02/066422, WO 02/070490, WO 02/076933, WO 03/024439, WO 03/072539, WO 03/091204, WO 04/016578, WO 2004/022547, WO 2004/037807, WO 2004/037773, WO 2004/037768, WO 2004/039762, WO 2004/039766, WO01/42193 and WO03/042160.

Suitable phosphodiesterase 4 (PDE4) inhibitors include compounds that are known to inhibit the PDE4 enzyme or which are discovered to act as a PDE4 inhibitor, and which are only PDE4 inhibitors, not compounds which inhibit other members of the PDE family as well as PDE4. Generally it is preferred to use a PDE4 inhibitor which has an IC_{50} ratio of about 0.1 or greater as regards the IC_{50} for the PDE4 catalytic form which binds rolipram with a high affinity divided by the IC_{50} for the form which binds rolipram with a low affinity. For the purposes of this disclosure, the cAMP catalytic site which binds R and S rolipram with a low affinity is denominated the "low affinity" binding site (LPDE 4) and the other form of this catalytic site which binds rolipram with a high affinity is denominated the "high affinity" binding site (HPDE 4). This term "HPDE4" should not be confused with the term "hPDE4" which is used to denote human PDE4.

A method for determining IC_{50}s ratios is set out in US patent 5,998,428 which is incorporated herein in full by reference as though set out herein. See also PCT application WO 00/51599 for another description of said assay.

Suitable PDE4 inhibitors include those compounds that have a salutary therapeutic ratio, i.e., compounds which preferentially inhibit cAMP catalytic activity where the enzyme is in the form that binds rolipram with a low affinity, thereby reducing the side effects that apparently are linked to inhibiting the form that binds rolipram with a high affinity. Another way to state this is that the preferred compounds will have an IC_{50} ratio of about 0.1 or greater as regards the IC_{50} for the PDE4 catalytic form that binds rolipram with a high affinity divided by the IC_{50} for the form that binds rolipram with a low affinity.

A further refinement of this standard is that of one wherein the PDE4 inhibitor has an IC_{50} ratio of about 0.1 or greater; said ratio is the ratio of the IC_{50} value for competing with the binding of 1nM of [^{3}H]R-rolipram to a form of PDE4 which binds rolipram with a high affinity over the IC_{50} value for

inhibiting the PDE4 catalytic activity of a form which binds rolipram with a low affinity using 1 μM[^{3}H]-cAMP as the substrate.

Most suitable are those PDE4 inhibitors which have an IC_{50} ratio of greater than 0.5, and particularly those compounds having a ratio of greater than 1.0. Preferred compounds are *cis* 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-carboxylic acid, 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-one and *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol]; these are examples of compounds which bind preferentially to the low affinity binding site and which have an IC_{50} ratio of 0.1 or greater.

Other suitable medicament compounds include: *cis*-4-cyano-4-[3-(cyclopentyloxy)-4-methoxyphenyl]cyclohexane-1-carboxylic acid (also known as cilomalast) disclosed in U.S. patent 5,552,438 and its salts, esters, pro-drugs or physical forms; AWD-12-281 from elbion (Hofgen, N. et al. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.98; CAS reference No. 247584020-9); a 9-benzyladenine derivative nominated NCS-613 (INSERM); D-4418 from Chiroscience and Schering-Plough; a benzodiazepine PDE4 inhibitor identified as CI-1018 (PD-168787) and attributed to Pfizer; a benzodioxole derivative disclosed by Kyowa Hakko in WO99/16766; K-34 from Kyowa Hakko; V-11294A from Napp (Landells, L.J. et al. Eur Resp J [Annu Cong Eur Resp Soc (Sept 19-23, Geneva) 1998] 1998, 12 (Suppl. 28): Abst P2393); roflumilast (CAS reference No 162401-32-3) and a pthalazinone (WO99/47505, the disclosure of which is hereby incorporated by reference) from Byk-Gulden; Pumafentrine, (-)-p-[(4*a*R*,10*b*S*)-9-ethoxy-1,2,3,4,4a,10b-hexahydro-8-methoxy-2-methylbenzo[c][1,6]naphthyridin-6-yl]-N,N-diisopropylbenzamide which is a mixed PDE3/PDE4 inhibitor which has been prepared and published on by Byk-Gulden, now Altana; arofylline under development by Almirall-Prodesfarma; VM554/UM565 from Vernalis; or T-440 (Tanabe Seiyaku; Fuji, K. et al. J Pharmacol Exp Ther,1998, 284(1): 162), and T2585.

Further compounds are disclosed in WO04/024728, WO04/056823 and WO04/103998, all of Glaxo Group Limited.

Suitable anticholinergic agents are those compounds that act as antagonists at the muscarinic receptor, in particular those compounds, which are antagonists of the M_1 or M_3 receptors, dual antagonists of the M_1/M_3 or M_2/M_3, receptors or pan-antagonists of the $M_1/M_2/M_3$ receptors. Exemplary compounds include the alkaloids of the belladonna plants as illustrated by the likes of atropine, scopolamine, homatropine, hyoscyamine; these compounds are normally administered as a salt, being tertiary amines.

Other suitable anti-cholinergics are muscarinic antagonists, such as (3-*endo*)-3-(2,2-di-2-thienylethenyl)-8,8-dimethyl-8-azoniabicyclo[3.2.1] octane iodide, (3-*endo*)-3-(2-cyano-2,2-diphenylethyl)-8,8-dimethyl-8-azoniabicyclo [3.2.1] octane bromide, 4-[hydroxy(diphenyl)methyl]-1-{2-[(phenylmethyl)oxy]ethyl}-1-azonia bicyclo[2.2.2] octane bromide, (1*R*,5*S*)-3-(2-cyano-2,2-diphenylethyl)-8-methyl-8-{2-[(phenylmethyl)oxy]ethyl}-8-azoniabicyclo[3.2.1] octane bromide, (*endo*)-3-(2-methoxy-2,2-di-thiophen-2-yl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide, (*endo*)-3-(2-cyano-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo [3.2.1]octane iodide, (*endo*)-3-(2-carbamoyl-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide, (*endo*)-3-(2-cyano-2,2-di-thiophen-2-yl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide, and (*endo*)-3-{2,2-diphenyl-3-[(1-phenyl-methanoyl)-amino]-propyl}-8,8-dimethyl-8-azonia-bicyclo[3.2.1] octane bromide.

Particularly suitable anticholinergics include ipratropium (e.g. as the bromide), sold under the name Atrovent, oxitropium (e.g. as the bromide) and tiotropium (e.g. as the bromide) (CAS-139404-48-1). Also of interest are: methantheline (CAS-53-46-3), propantheline bromide (CAS- 50-34-9), anisotropine methyl bromide or Valpin 50 (CAS- 80-50-2), clidinium bromide (Quarzan, CAS-3485-62-9), copyrrolate (Robinul), isopropamide iodide (CAS-71-81-8), mepenzolate bromide (U.S. patent 2,918,408), tridihexethyl chloride

(Pathilone, CAS-4310-35-4), and hexocyclium methylsulfate (Tral, CAS-115-63-9). See also cyclopentolate hydrochloride (CAS-5870-29-1), tropicamide (CAS-1508-75-4), trihexyphenidyl hydrochloride (CAS-144-11-6), pirenzepine (CAS-29868-97-1), telenzepine (CAS-80880-90-9), AF-DX 116, or methoctramine, and the compounds disclosed in WO01/04118. Also of interest are revatropate (for example, as the hydrobromide, CAS 262586-79-8) and LAS-34273 which is disclosed in WO01/04118, darifenacin (CAS 133099-04-4, or CAS 133099-07-7 for the hydrobromide sold under the name Enablex), oxybutynin (CAS 5633-20-5, sold under the name Ditropan), terodiline (CAS 15793-40-5), tolterodine (CAS 124937-51-5, or CAS 124937-52-6 for the tartrate, sold under the name Detrol), otilonium (for example, as the bromide, CAS 26095-59-0, sold under the name Spasmomen), trospium chloride (CAS 10405-02-4) and solifenacin (CAS 242478-37-1, or CAS 242478-38-2 for the succinate also known as YM-905 and sold under the name Vesicare).

Other anticholinergic agents include compounds disclosed in USSN 60/487,981 and USSN 60/511,009.

Suitable antihistamines (also referred to as H_1-receptor antagonists) include any one or more of the numerous antagonists known which inhibit H_1-receptors, and are safe for human use. All are reversible, competitive inhibitors of the interaction of histamine with H_1-receptors. Examples include ethanolamines, ethylenediamines, and alkylamines. In addition, other first generation antihistamines include those which can be characterized as based on piperizine and phenothiazines. Second generation antagonists, which are non-sedating, have a similar structure-activity relationship in that they retain the core ethylene group (the alkylamines) or mimic the tertiary amine group with piperizine or piperidine.

Examples of H1 antagonists include, without limitation, amelexanox, astemizole, azatadine, azelastine, acrivastine, brompheniramine, cetirizine, levocetirizine, efletirizine, chlorpheniramine, clemastine, cyclizine, carebastine, cyproheptadine, carbinoxamine, descarboethoxyloratadine, doxylamine,

dimethindene, ebastine, epinastine, efletirizine, fexofenadine, hydroxyzine, ketotifen, loratadine, levocabastine, mizolastine, mequitazine, mianserin, noberastine, meclizine, norastemizole, olopatadine, picumast, pyrilamine, promethazine, terfenadine, tripelennamine, temelastine, trimeprazine and triprolidine, particularly cetirizine, levocetirizine, efletirizine and fexofenadine.

Exemplary H1 antagonists are as follows:

Ethanolamines: carbinoxamine maleate, clemastine fumarate, diphenylhydramine hydrochloride, and dimenhydrinate;

Ethylenediamines: pyrilamine amleate, tripelennamine HCl, and tripelennamine citrate;

Alkylamines: chlropheniramine and its salts such as the maleate salt, and acrivastine;

Piperazines: hydroxyzine HCl, hydroxyzine pamoate, cyclizine HCl, cyclizine lactate, meclizine HCl, and cetirizine HCl;

Piperidines: Astemizole, levocabastine HCl, loratadine or its descarboethoxy analogue, and terfenadine and fexofenadine hydrochloride or another pharmaceutically acceptable salt.

Azelastine hydrochloride is yet another H_1 receptor antagonist which may be used in combination with a PDE4 inhibitor.

The medicament, or one of the medicaments, may be an H3 antagonist (and/or inverse agonist). Examples of H3 antagonists include, for example, those compounds disclosed in WO2004/035556 and in WO2006/045416.

Other histamine receptor antagonists which may be used include antagonists (and/or inverse agonists) of the H4 receptor, for example, the compounds disclosed in Jablonowski *et al.*, *J. Med. Chem.* 46:3957-3960 (2003).

In respect of combination products, co-formulation compatibility is generally determined on an experimental basis by known methods and may depend on chosen type of medicament dispenser device action.

The medicament components of a combination product are suitably selected from the group consisting of anti-inflammatory agents (for example a corticosteroid or an NSAID), anticholinergic agents (for example, an M_1, M_2, M_1/M_2 or M_3 receptor antagonist), other β_2-adrenoreceptor agonists, antiinfective agents (e.g. an antibiotic or an antiviral), and antihistamines. All suitable combinations are envisaged.

Suitably, the co-formulation compatible components comprise a β_2-adrenoreceptor agonist and a corticosteroid; and the co-formulation incompatible component comprises a PDE-4 inhibitor, an anti-cholinergic or a mixture thereof. The β_2-adrenoreceptor agonists may for example be salbutamol (e.g., as the free base or the sulphate salt) or salmeterol (e.g., as the xinafoate salt) or formoterol (eg as the fumarate salt). The corticosteroid may for example, be a beclomethasone ester (e.g., the dipropionate) or a fluticasone ester (e.g., the propionate) or budesonide.

In one example, the co-formulation compatible components comprise fluticasone propionate and salmeterol, or a salt thereof (particularly the xinafoate salt) and the co-formulation incompatible component comprises a PDE-4 inhibitor, an anti-cholinergic (e.g. ipratropium bromide or tiotropium bromide) or a mixture thereof.

In another example, the co-formulation compatible components comprise budesonide and formoterol (e.g. as the fumarate salt) and the co-formulation incompatible component comprises a PDE-4 inhibitor, an anti-cholinergic (e.g. ipratropium bromide or tiotropium bromide) or a mixture thereof.

Generally, powdered medicament particles suitable for delivery to the bronchial or alveolar region of the lung have an aerodynamic diameter of less than 10 micrometers, preferably from 1-6 micrometers. Other sized particles may be used if delivery to other portions of the respiratory tract is desired, such as the nasal cavity, mouth or throat. The medicament may be delivered as pure drug, but more appropriately, it is preferred that medicaments are delivered

together with excipients (carriers) which are suitable for inhalation. Suitable excipients include organic excipients such as polysaccharides (i.e. starch, cellulose and the like), lactose, glucose, mannitol, amino acids, and maltodextrins, and inorganic excipients such as calcium carbonate or sodium chloride. Lactose is a preferred excipient.

Particles of powdered medicament and/or excipient may be produced by conventional techniques, for example by micronisation, milling or sieving. Additionally, medicament and/or excipient powders may be engineered with particular densities, size ranges, or characteristics. Particles may comprise active agents, surfactants, wall forming materials, or other components considered desirable by those of ordinary skill.

The excipient may be included with the medicament via well-known methods, such as by admixing, co-precipitating and the like. Blends of excipients and drugs are typically formulated to allow the precise metering and dispersion of the blend into doses. A standard blend, for example, contains 13000 micrograms lactose mixed with 50 micrograms drug, yielding an excipient to drug ratio of 260:1. Dosage blends with excipient to drug ratios of from 100:1 to 1:1 may be used. At very low ratios of excipient to drug, however, the drug dose reproducibility may become more variable.

The medicament dispenser device described herein is in one aspect suitable for dispensing medicament for the treatment of respiratory disorders such as disorders of the lungs and bronchial tracts including asthma, bronchitis, chest infections and chronic obstructive pulmonary disorder (COPD). In another aspect, the invention is suitable for dispensing medicament for the treatment of a condition requiring treatment by the systemic circulation of medicament, for example migraine, diabetes, pain relief e.g. inhaled morphine.

Accordingly, there is provided the use of the medicament dispenser device herein for the treatment of a respiratory disorder, such as asthma and COPD. Alternatively, the present invention provides a method of treating a respiratory disorder such as, for example, asthma and COPD, which comprises

administration by inhalation of an effective amount of medicament product as herein described from a medicament dispenser device herein.

The amount of any particular medicament compound or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof which is required to achieve a therapeutic effect will, of course, vary with the particular compound, the route of administration, the subject under treatment, and the particular disorder or disease being treated. The medicaments for treatment of respiratory disorders herein may for example, be administered by inhalation at a dose of from 0.0005mg to 10 mg, preferably 0.005mg to 0.5mg. The dose range for adult humans is generally from 0.0005 mg to 100mg per day and preferably 0.01 mg to 1.5mg per day.

It will be understood that the present disclosure is for the purpose of illustration only and the invention extends to modifications, variations and improvements thereto.

It will further be appreciated that the 'summary of the invention' section above discloses additional details, modifications or adaptations for the exemplary medicament dispenser devices, medicament pack(s) and manifolds described with reference to the accompanying Figures.

Where not stated, the components of the medicament dispenser devices herein may be made from conventional engineering materials, especially conventional engineering plastics materials, more especially those which allow moulding of the component.

The application of which this description and claims form part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described therein. They may take the form of product, method or use claims and may include, by way of example and without limitation, one or more of the following claims:

The above embodiments are to be understood as illustrative examples of the invention. Further embodiments of the invention are envisaged. For

example, the sensor arrangement may be capable of detecting a magnetic signal. Also some part or all of the electronic circuitry may be printed on the plastic material of the manifold.

Whilst the medicament dispenser of the present invention has been described in relation to a dispenser comprising two medicament packs, it should be appreciated that that same dispenser may be used with a single medicament pack with one of the dispensing mechanisms not acting on any medicament pack. Alternatively, each medicament pack could contain the same medicament powder (i.e. same active or combination of actives).

It is to be understood that any feature described in relation to any one embodiment may be used alone, or in combination with other features described, and may also be used in combination with one or more features of any other of the embodiments, or any combination of any other of the embodiments. Furthermore, equivalents and modifications not described above may also be employed without departing from the scope of the invention, which is defined in the accompanying claims.

Claims

1. A medicament dispenser for dispensing medicament from a medicament pack, said medicament pack having a first structure, a second structure which is secured to said first structure and which is intended to be separated from said first structure to enable release of medicament from spaced-apart medicament locations enclosed by the first and second structures, said second structure having a laminated construction and comprising a metallic layer and a non-metallic layer, said medicament dispenser comprising:

(i) an internal dispensing mechanism for separating said second structure from the first structure to expose said medicament locations and advance the separated first and second structures on respective first and second paths in the dispenser; and

(ii) an outlet at which a user is able to receive medicament from the exposed medicament locations,

wherein the medicament dispenser is provided with a fault detector adapted to detect a fault condition in which medicament is potentially not being released, said fault detector comprising a sensor associated with said second path, said sensor being capable of detecting an absence of said metallic layer in said second path and being adapted to produce an output signal based on said detected absence.

2. A medicament dispenser according to claim 1, said laminated construction of said second structure having said metallic layer beneath an outer layer, wherein said fault detector is adapted to detect delamination of said outer layer from said second structure so that on operation of the internal dispensing mechanism the outer layer is advanced on the second path while the metallic layer is advanced on said first path with the first structure.

3. A medicament dispenser according to claim 1 or 2, said fault detector being capable of detecting incidence of a predetermined electromagnetic radiation signal thereupon.

4. A medicament dispenser according to claim 3, said fault detector being capable of detecting relative transparencies of material in said first and second paths to said predetermined electromagnetic radiation signal.

5. A medicament dispenser according to claim 3 or 4, said fault detector comprises a radiation source for said predetermined electromagnetic radiation signal.

6. A medicament dispenser according to claim any one of claims 3 to 5, said predetermined electromagnetic radiation is light radiation.

7. A medicament dispenser according to claim 6, said light radiation comprising predominantly infra-red light radiation.

8. A medicament dispenser according to any one of claims 5 to 7, said sensor is disposed on one side of the second path and the dispenser is configured and arranged so that the radiation from said source is transmitted across the second path towards the sensor.

9. A medicament dispenser according to any one of claims 5 to 8, said fault detector comprises a radiation guide on the opposing side of the second path from the sensor and the radiation is conveyed along said guide.

10. A medicament dispenser according to claim 9, wherein said radiation guide is provided by at least a part of the outlet.

11. A medicament dispenser according to any preceding claim, wherein said first structure comprises a container at each medicament location for containing the medicament located thereat and the second structure forms a cover for said containers.

12. A medicament dispenser according to any preceding claim, wherein said medicament pack is in the form of an elongate strip.

13. A medicament dispenser according to any preceding claim, wherein said first structure is a base sheet of said strip and the second structure is a cover sheet of the strip.

14. A medicament dispenser according to any preceding claim, wherein said second structure is peelably separable from the first structure.

15. A medicament dispenser according to any preceding claim, wherein said dispenser is an inhalation device.

16. A medicament dispenser according to any preceding claim, wherein said medicament is a medicament powder.

17. A medicament dispenser according to any preceding claim, wherein said dispenser comprises plural such medicament packs, each with a respective second path, and the fault detector is adapted to detect the absence of said metallic layer of any one of the packs in the respective second path.

18. A medicament dispenser according to claim 17, wherein said fault detector comprises a sensor disposed to one side of each said second path.

19. A medicament dispenser according to claim 17 or 18, wherein said fault detector comprises a single radiation source.

20. A medicament dispenser according to any preceding claim, wherein said fault detector further comprises a detection module to detect a level of ambient light signal in said dispenser and said fault detector being capable of determining a resulting signal taking into account said detected ambient light.

21. A medicament dispenser for dispensing medicament from a medicament pack, said medicament pack having a first structure, a second structure which is secured to said first structure and which is intended to be separated from said first structure to enable release of medicament from spaced-apart medicament locations enclosed by the first and second structures, said medicament dispenser comprising:

(i) an internal dispensing mechanism for separating said second structure from the first structure to expose said medicament locations and advance the separated first and second structures on respective first and second paths in the dispenser; and

(ii) an outlet at which a user is able to receive medicament from the exposed medicament locations,

wherein the medicament dispenser is provided with a fault detector adapted to detect a fault condition,

said medicament dispenser being further provided with a locking mechanism, said locking mechanism being adapted to move in response to an electrical drive input from a non-locking position to a locking position in the event that said fault condition is detected.

22. A medicament dispenser according to claim 21, said locking mechanism being arranged to prevent further use of the medicament dispenser in said locking position, by locking with one or more elements of said dispenser.

23. A medicament dispenser according to claim 22, said locking mechanism being arranged to lock with one or more elements of said internal dispensing mechanism of said dispenser.

24. A medicament dispenser according to claim 21 or 22, wherein said internal dispensing mechanism is actuable by a movable mouthpiece cover such that movement of said cover from a closed position, in which said mouthpiece is covered, to an opened position, in which said mouthpiece is uncovered, results in actuation of said internal dispensing mechanism, said locking mechanism being arranged to lock with an element of said mouthpiece cover.

25. A medicament dispenser according to any one of claims 21 to 24, said internal dispensing mechanism comprising a driver for advancing said separated second structure on said second path, said locking mechanism comprising a pin being located in a cavity of said driver and a biasing mechanism for biasing said pin out of the cavity, said pin being adapted to move from a non-locking position, in which said pin is retracted in said driver cavity, into a locking position in which said pin projects out of said driver cavity to lock with one or more elements of said dispenser.

26. A medicament dispenser according to any one of claims 21 to 25, said locking mechanism comprising an actuator, said actuator being designed to maintain said locking mechanism in said non-locking position and to release said locking mechanism for movement to said locking position in the event that said condition is detected.

27. A medicament dispenser according to any one of claims 21 to 26, said fault detector and said locking mechanism being energised by an energising module which is located in said dispenser.

28. A medicament dispenser according to claim 27, said energising module being activated by said mouthpiece cover when said mouthpiece cover is moved from said closed position to said opened position.

29. A medicament dispenser according to claim 28, said energising module being subsequently deactivated after a specific amount of time when said mouthpiece cover is kept in said opened position.

30. A method for detecting a fault condition in a medicament dispenser for dispensing medicament from a medicament pack of said dispenser, wherein:

(a) said medicament pack has:

(i) a first structure; and

(ii) a second structure which is secured to said first structure and which is intended to be separated from said first structure to enable release of medicament from spaced-apart medicament locations enclosed by the first and second structures;

(b) said medicament dispenser comprises:

(i) an internal dispensing mechanism for separating said second structure from the first structure to expose said medicament locations and advance the separated first and second structures on respective first and second paths in the dispenser; and

(ii) an outlet at which a user is able to receive medicament from the exposed medicament locations;

(c) said fault condition is failure to separate the second structure from the first structure on operation of said internal dispensing mechanism resulting in

medicament locations remaining enclosed by the first structure and at least a part of the second structure so that the medicament thereat is not releasable and said at least a part of the second structure is not advanced on said second path; and

(d) the method comprises the step of providing the medicament dispenser with a fault detector adapted to detect the absence of at least a part of the second structure in the second path.

31. A method according to claim 30, said fault detector being an electronic fault detector.

32. A method according to claim 30 or 31, wherein said second structure has a laminated construction with an inner layer secured to said first structure to cover the medicament locations and an outer layer, wherein the fault condition is delamination of said outer layer from said inner layer so that on operation of the internal dispensing mechanism the outer layer is advanced on the second path while the inner layer is advanced on said first path covering the medicament locations and wherein the fault detector is adapted to detect the absence of the inner layer from the second path.

33. A method according to claim 32, wherein said inner layer has a property which is different from that in the outer layer and the fault detector is adapted to detect the absence of said inner layer based on said property difference.

34. A method according to claim 33, wherein the property of the inner layer is found in the first structure.

35. A method according to claim 33 or 34, wherein the property is a material comprised in the inner layer which is not comprised in the outer layer.

36. A method according to claim 35, wherein said material is a metallic material.

37. A method according to any one of claims 33 to 36, wherein the property is the relative responses of the inner and outer layers to incidence of a predetermined electromagnetic radiation signal thereupon.

38. A method according to claim 37, wherein the property is the relative transparencies of the inner and outer layers to said predetermined electromagnetic radiation signal.

39. A method according to claim 37 or 38, wherein said predetermined electromagnetic radiation is light radiation.

40. A method according to any one of claims 30 to 39, wherein said fault detector comprises a sensor associated with the second path to detect the absence of at least a part of the second structure.

41. A method according to claim 40, wherein said sensor is adapted to produce an output signal based on said detected absence.

42. A method according to any one of claims 37 to 39 or either of claims 40 and 41 when dependent on any one of claims 37 to 39, wherein said fault detector comprises a source for said electromagnetic radiation signal.

43. A method according to claim 42 when dependent on claim 40 or 41, wherein said sensor is disposed on one side of the second path and the dispenser is configured and arranged so that the radiation from said source is transmitted across the second path towards the sensor.

44. A method according to claim 43, wherein said fault detector comprises a radiation guide on the opposing side of the second path from the sensor and the radiation is conveyed along said guide.

45. A method according to claim 44, wherein said guide is provided by at least a part of the outlet.

46. A method according to any one of claims 30 to 45, wherein said first structure comprises a container at each medicament location for containing the medicament located thereat and the second structure forms a cover for said containers.

47. A method according to any one of claims 30 to 46, wherein said medicament pack is in the form of an elongate strip.

48. A method according to any one of claims 30 to 47, wherein said first structure is a base sheet of said strip and the second structure is a cover sheet of the strip.

49. A method according to any one of claims 30 to 48, wherein said second structure is peelably separable from the first structure.

50. A method according to any one of claims 30 to 49, wherein said dispenser is an inhalation device.

51. A method according to any one of claims 30 to 50, wherein said medicament is a medicament powder.

52. A method according to any one of claims 30 to 51, wherein said dispenser comprises plural such medicament packs, each with a respective second path, and the fault detector is adapted to detect the absence of the least a part of the second structure of any one of the packs in the respective second path.

53. A method according to claim 52, wherein said fault detector comprises a sensor disposed to one side of each said second path.

54. A method according to claim 52 or 53, wherein said fault detector comprises a single radiation source.

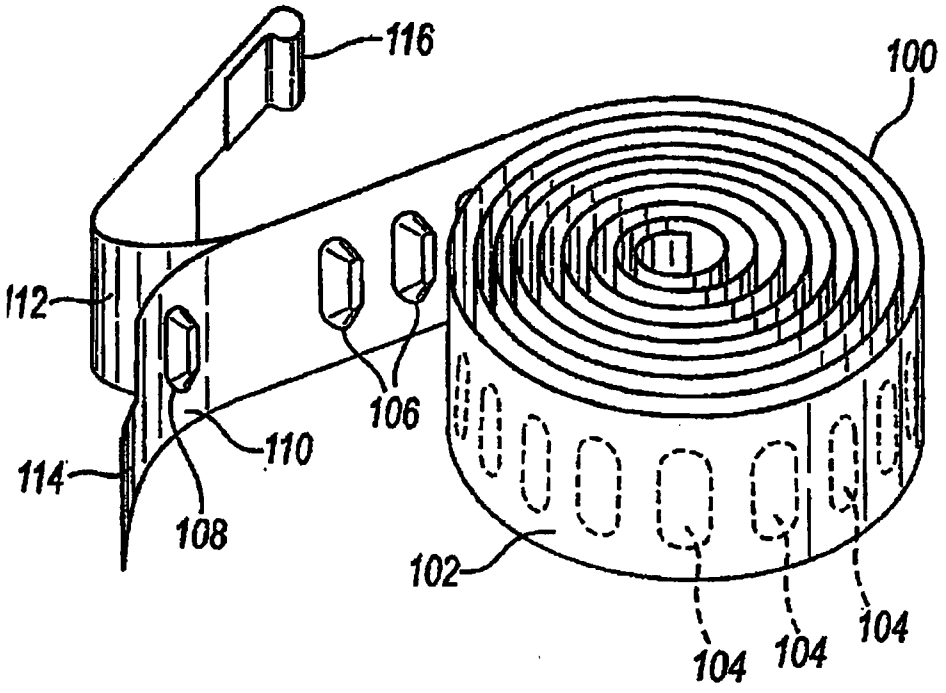

FIG. 1

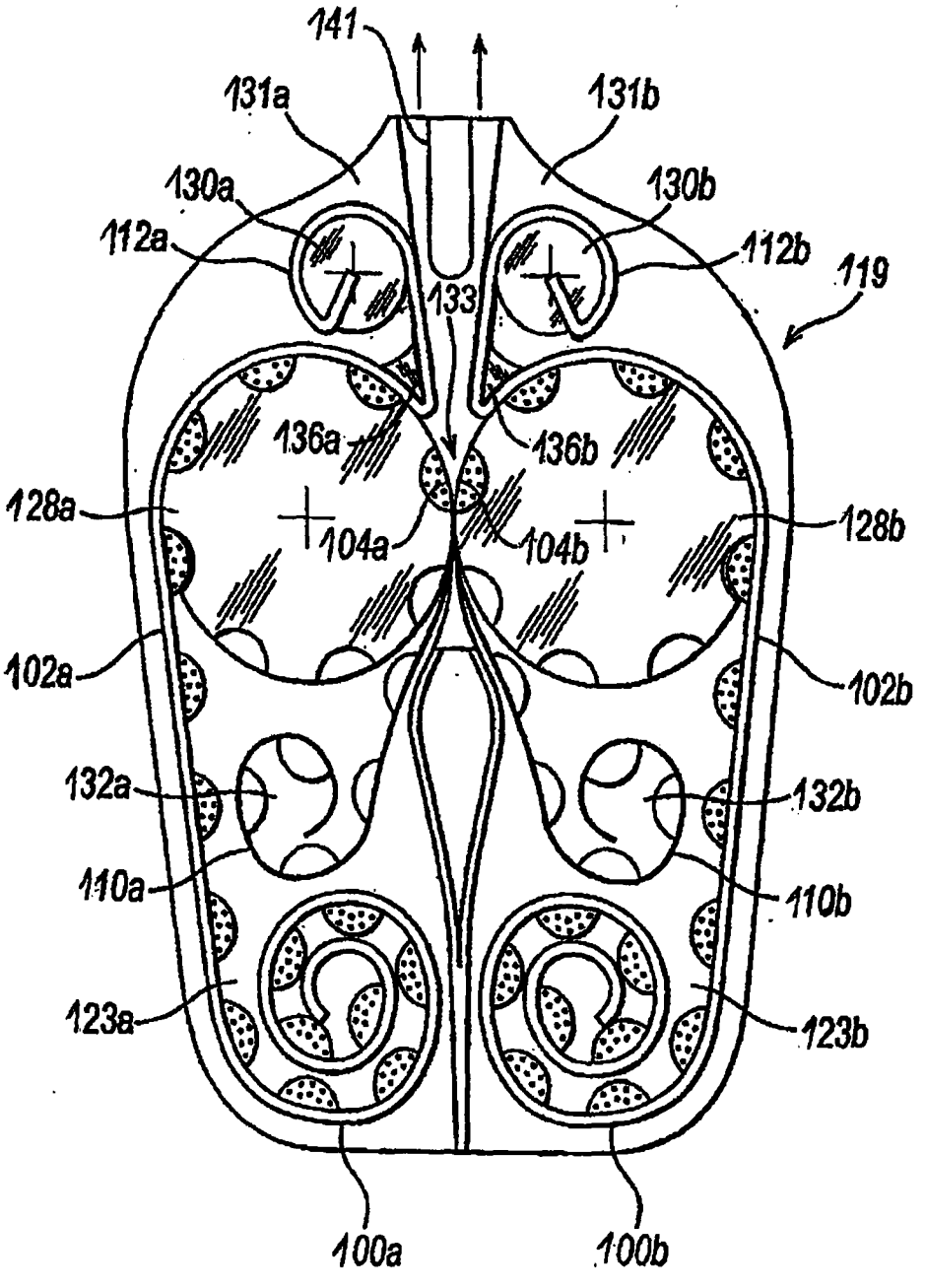
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FIG. 2

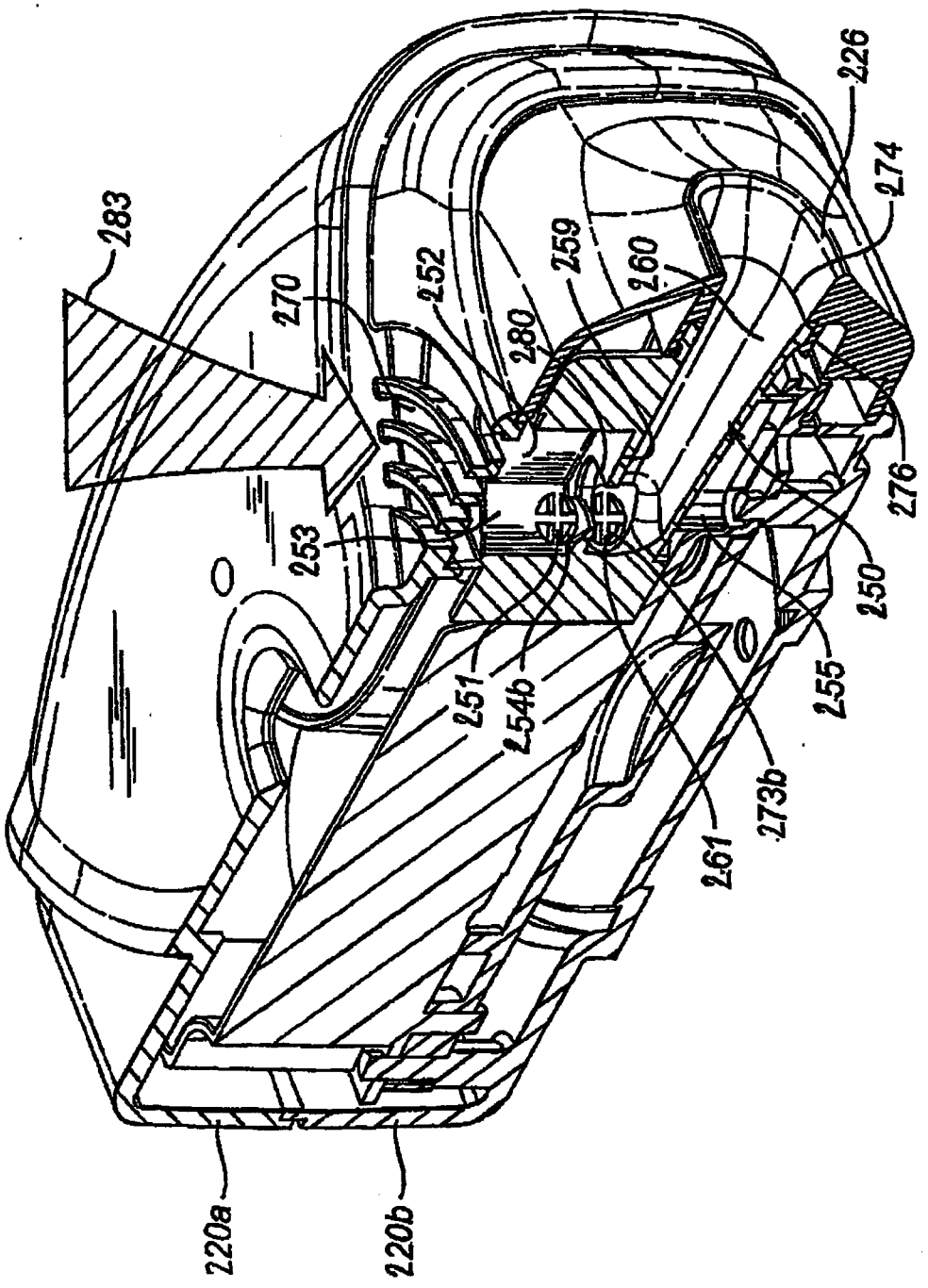
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FIG. 3

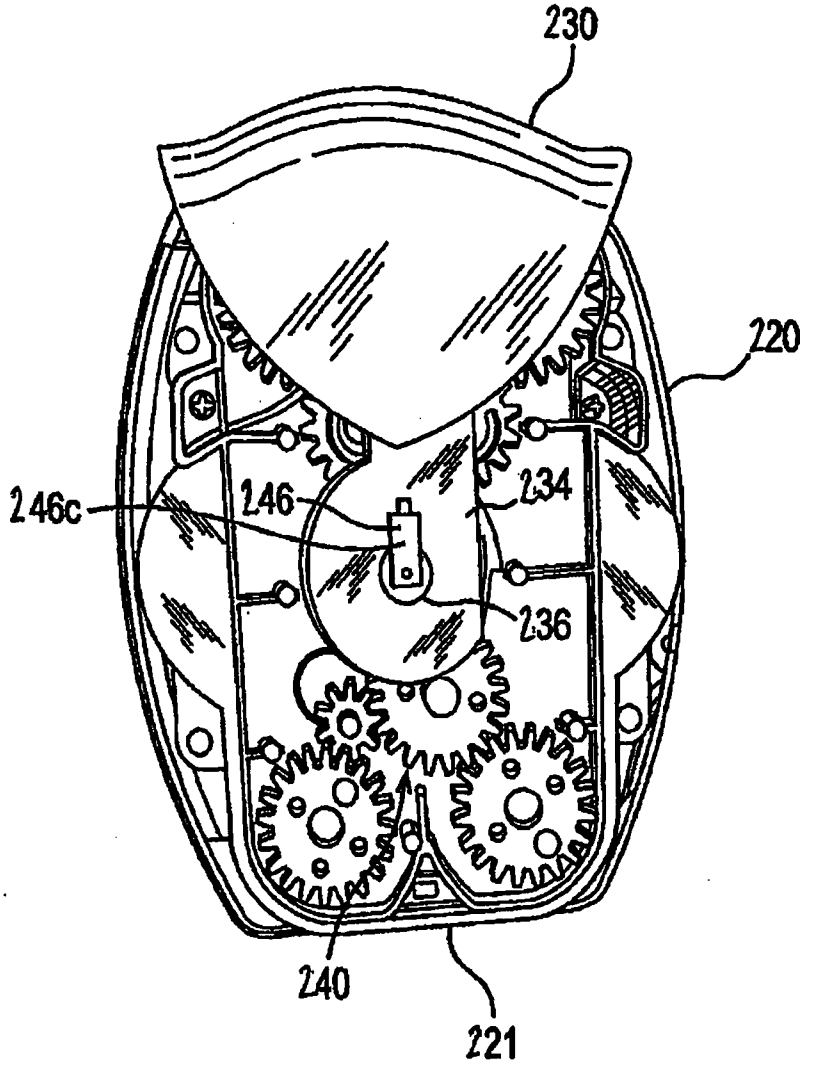

FIG. 4a

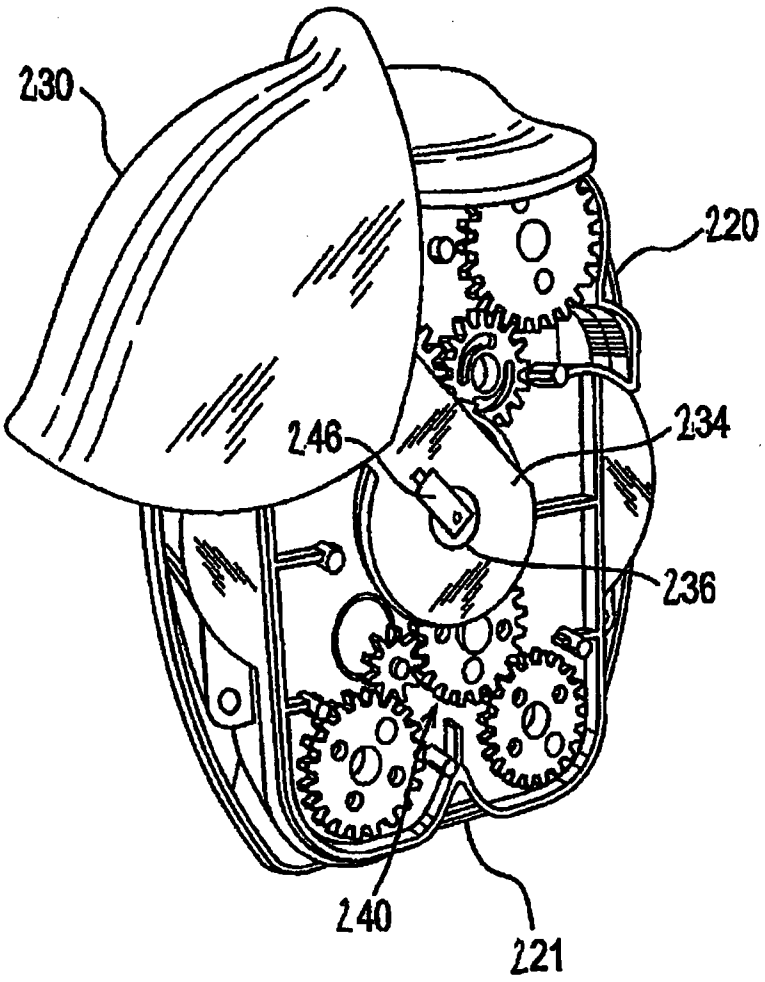

FIG. 4b

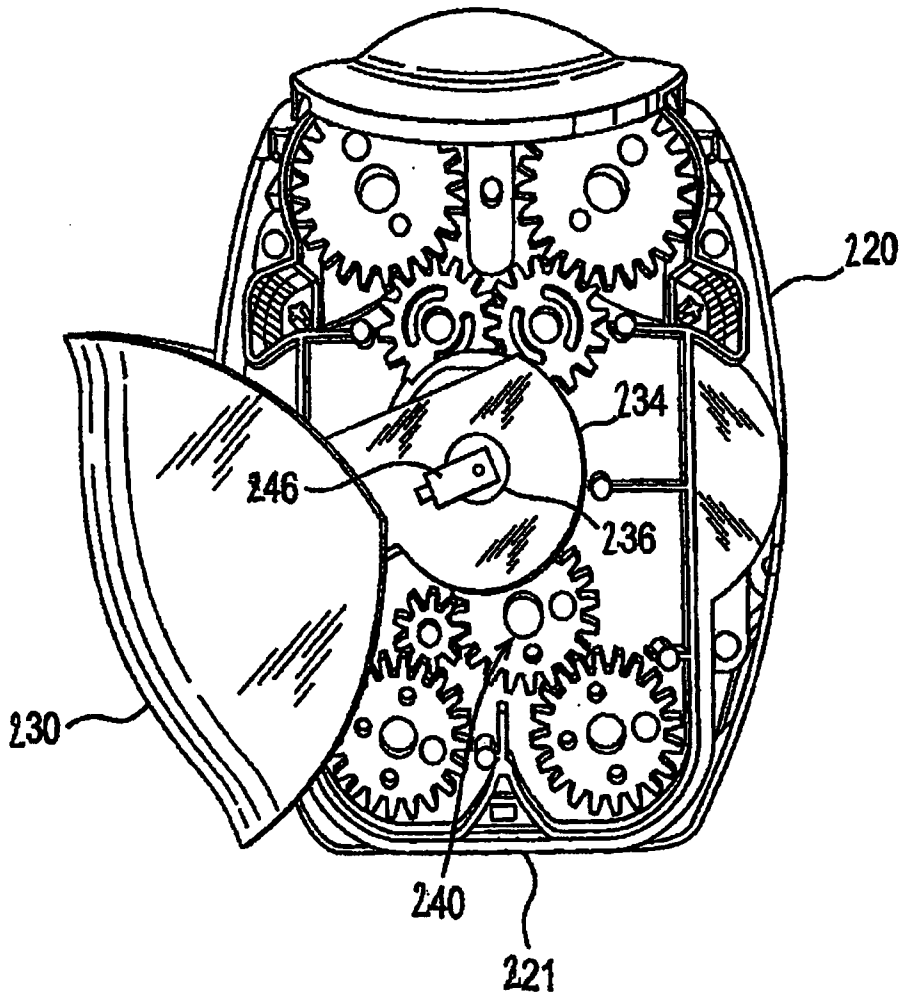

FIG. 4c

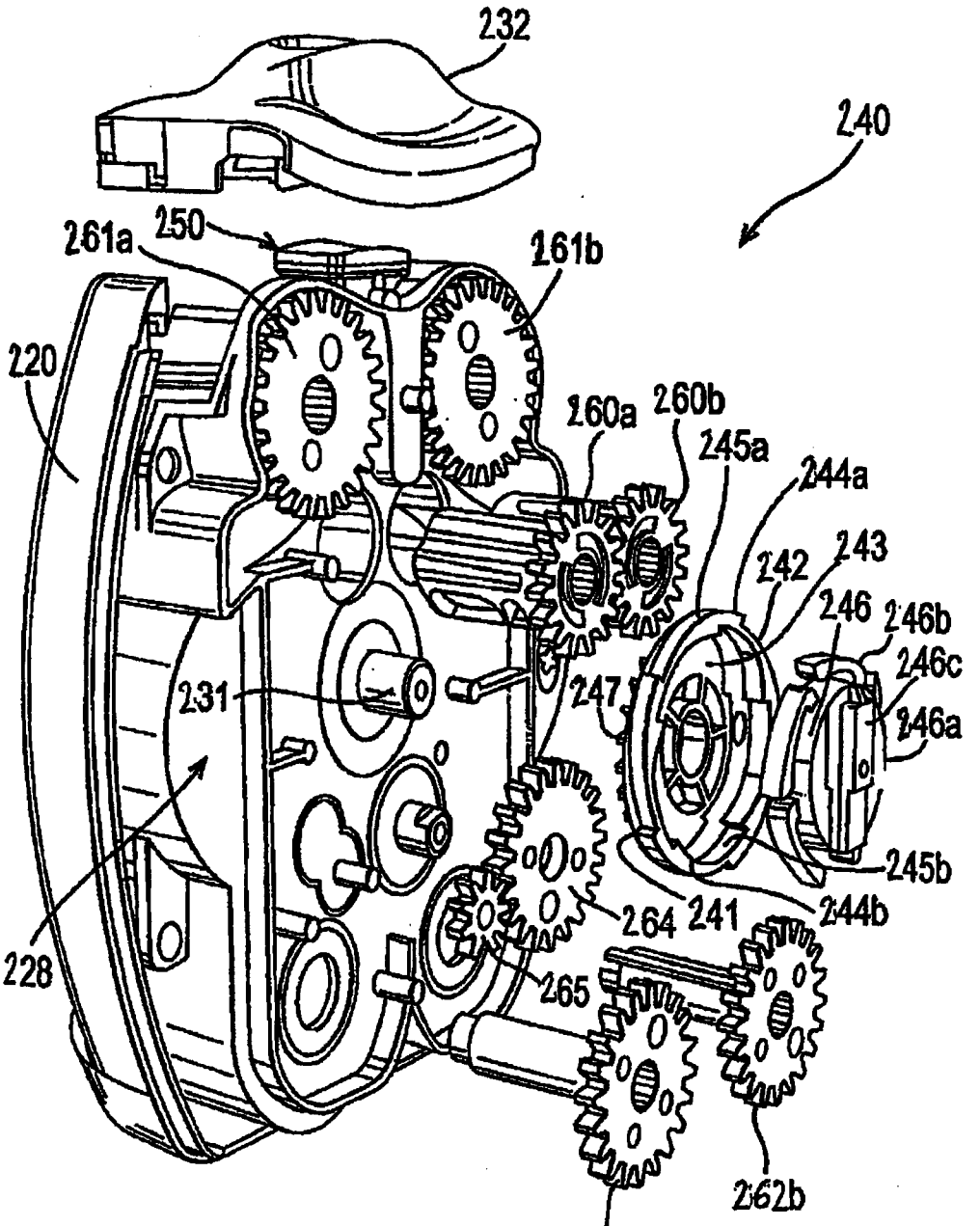
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FIG. 5a

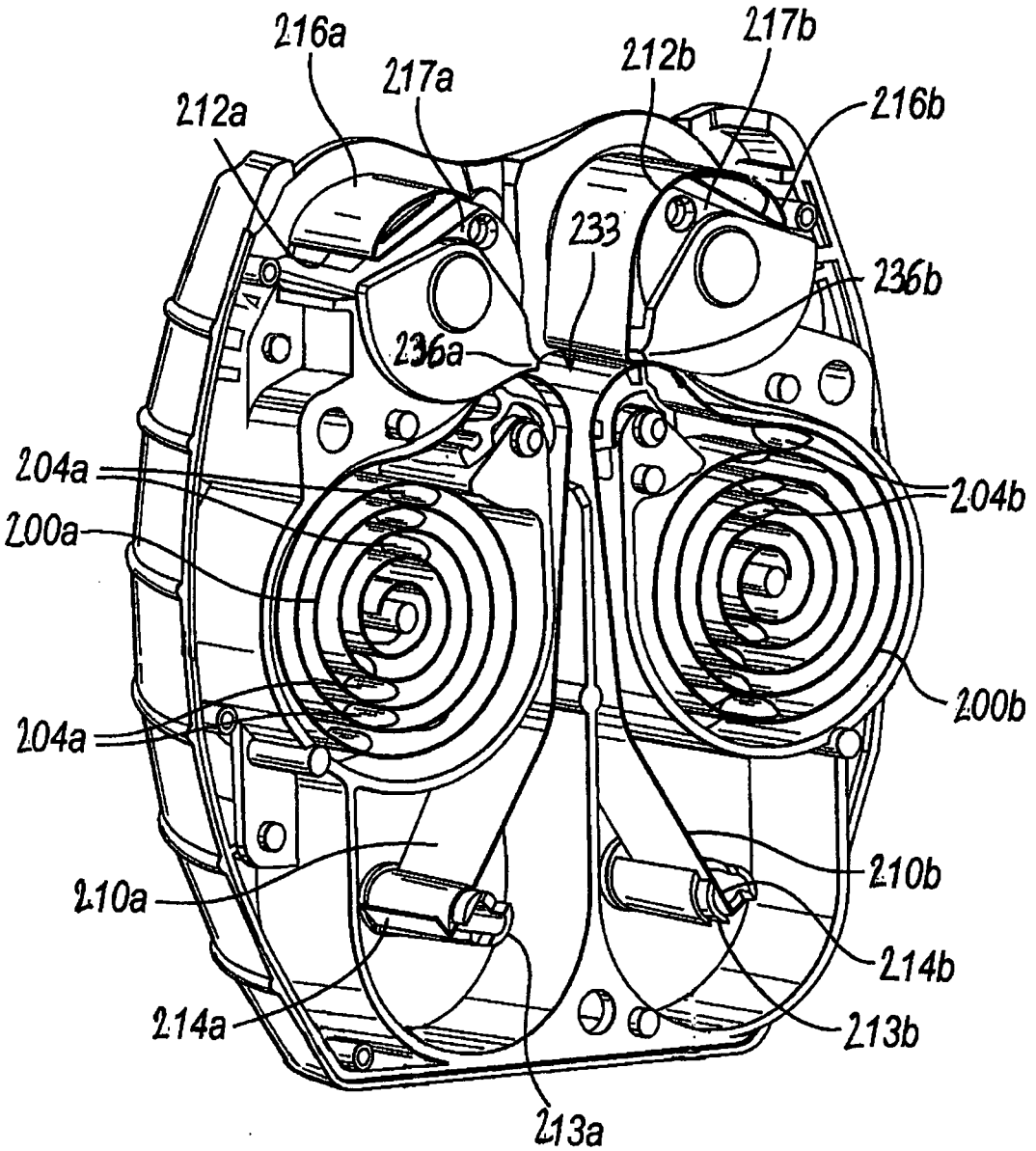
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FIG. 5b

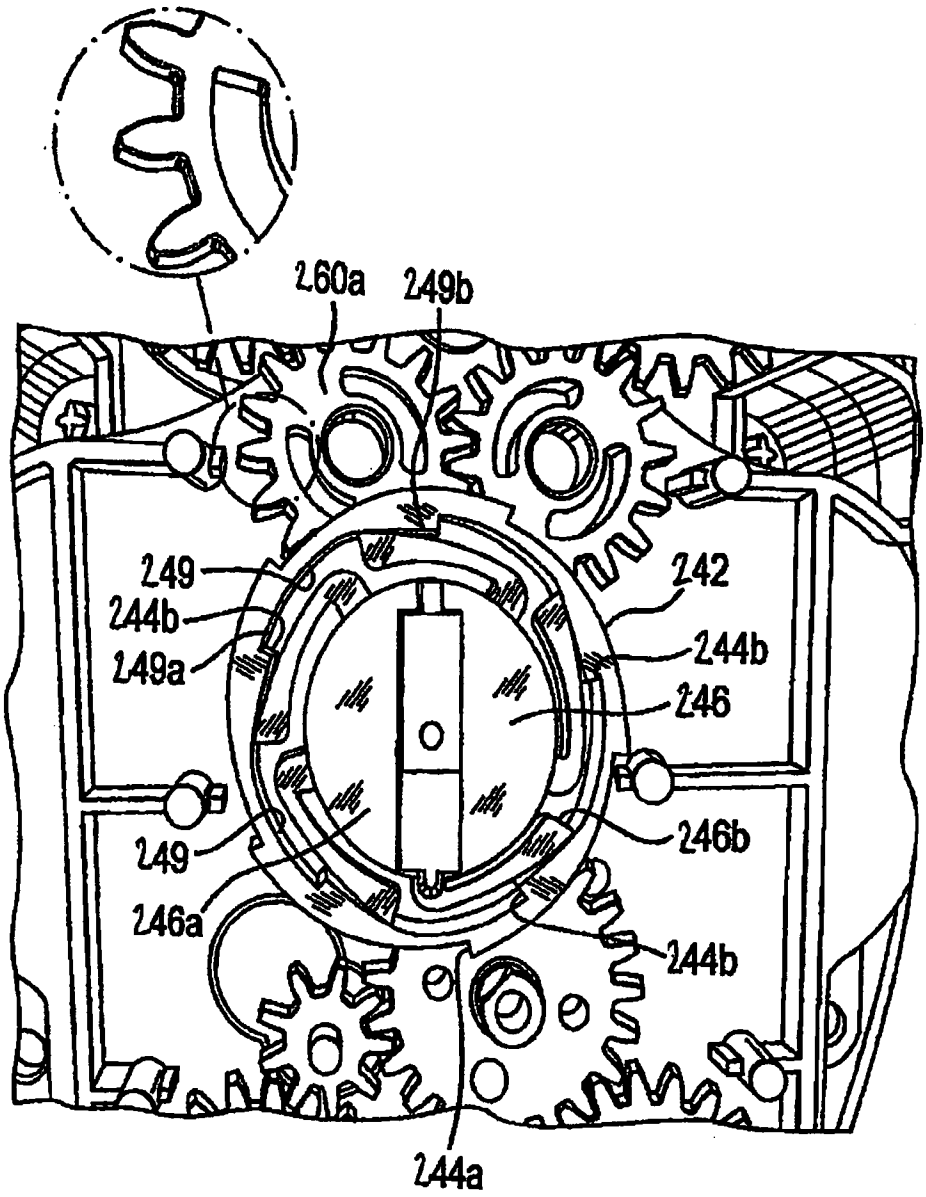


FIG. 6a

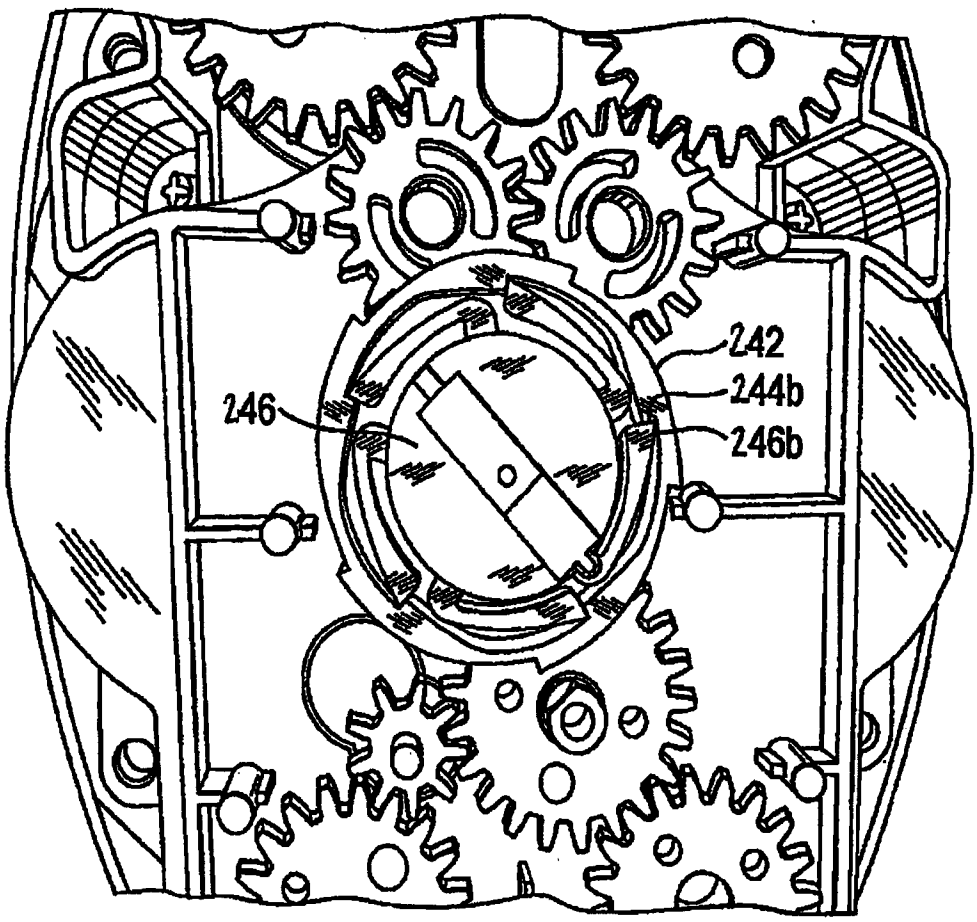


FIG. 6b

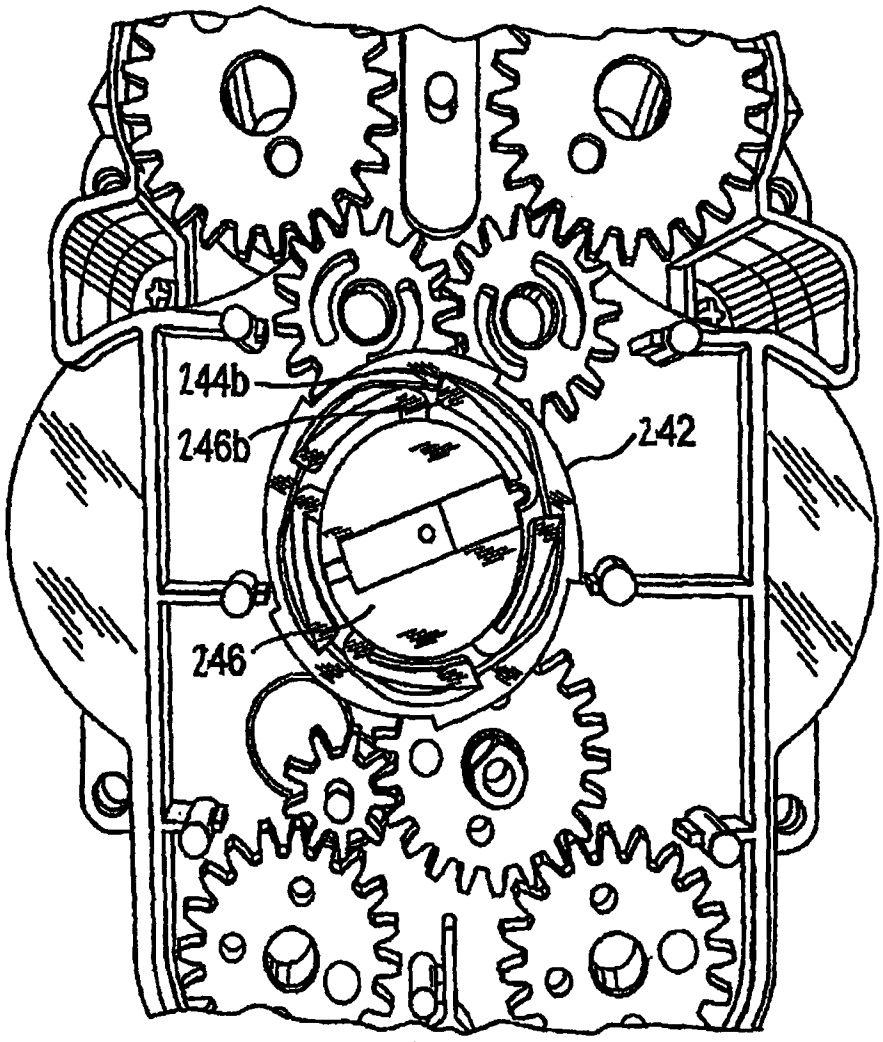


FIG. 6c

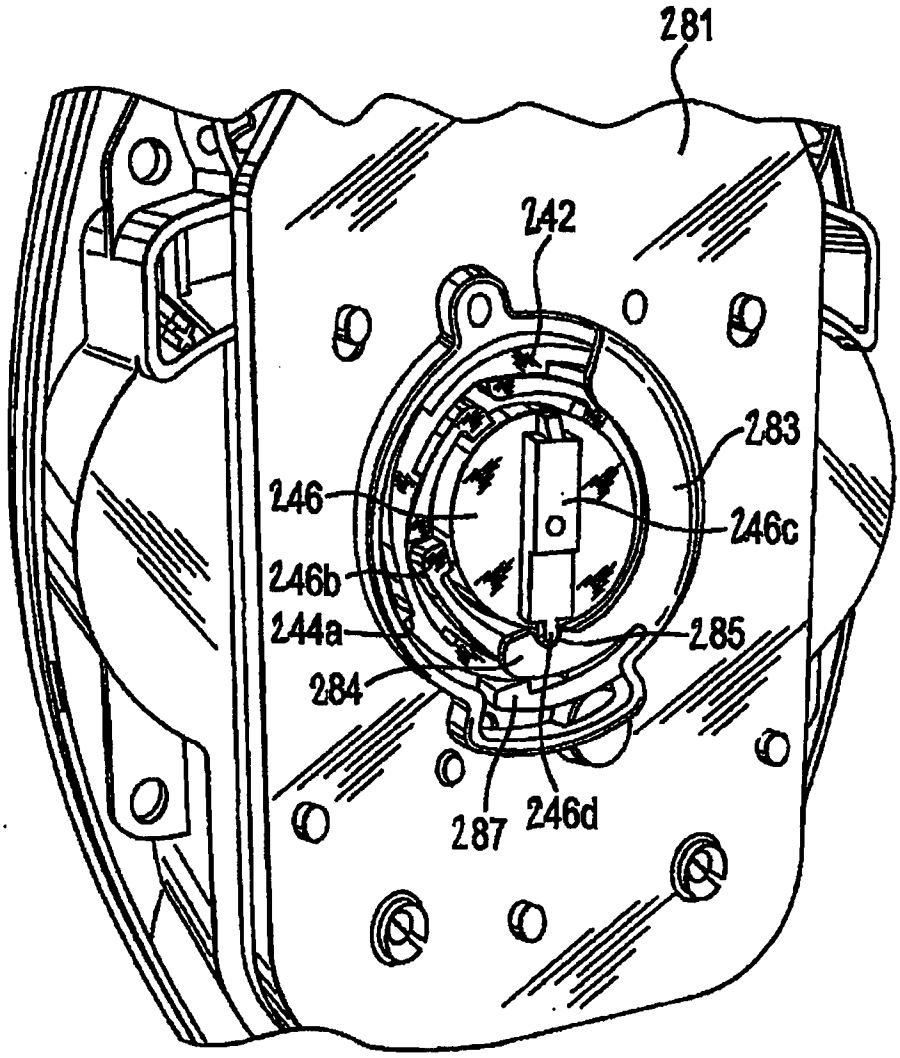


FIG. 7

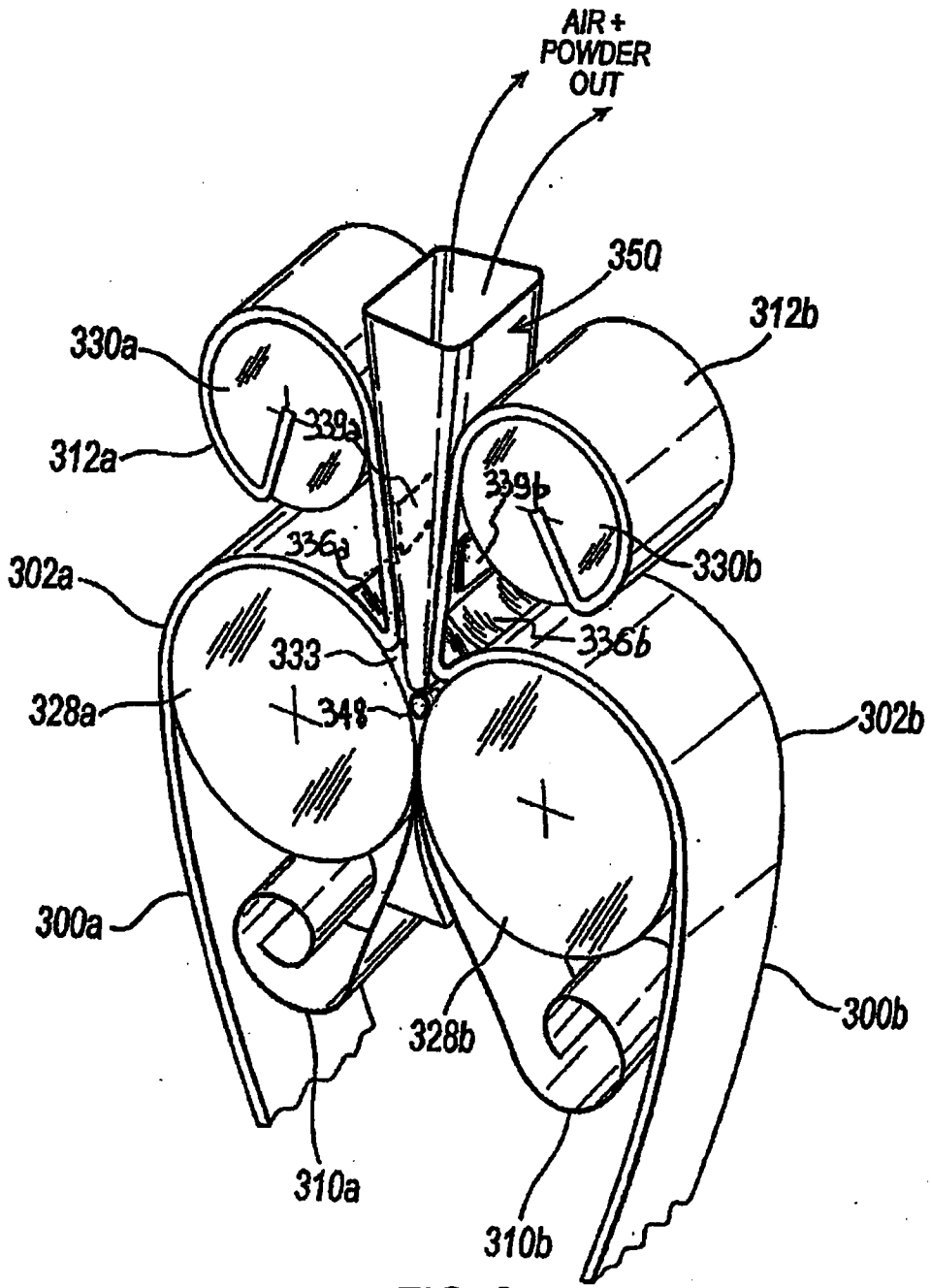

AIR + POWDER OUT
350
312b
330a
338a
312a
339b
336a
330b
302a
333
336b
328a
348
302b
300a
328b
300b
310a
310b

FIG. 8

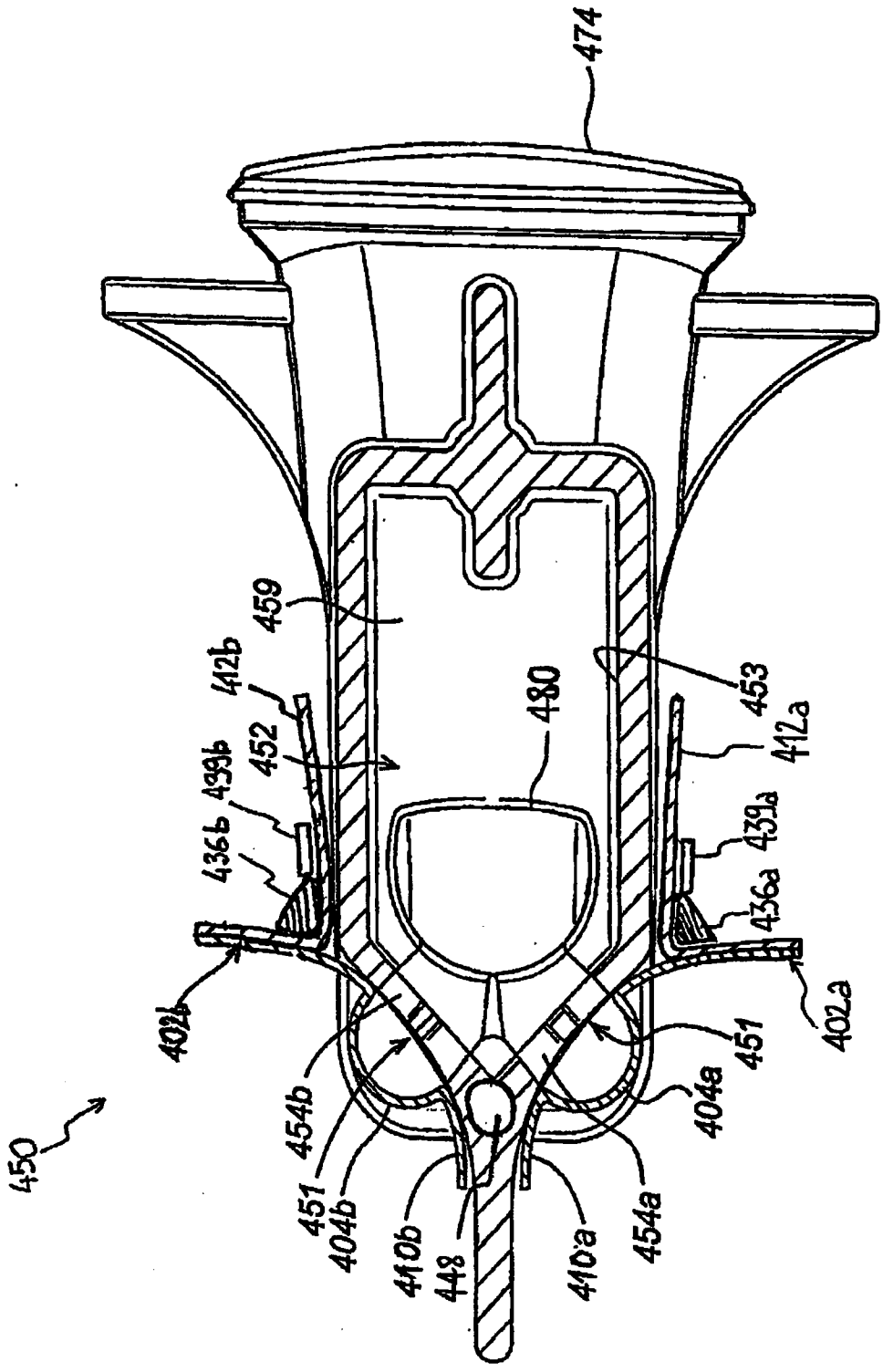

474
459
412b
439b
452
436b
402b
454b
451
404b
410b
448
410a
454a
404a
451
402a
436a
439a
412a
453
480
450

FIG. 9

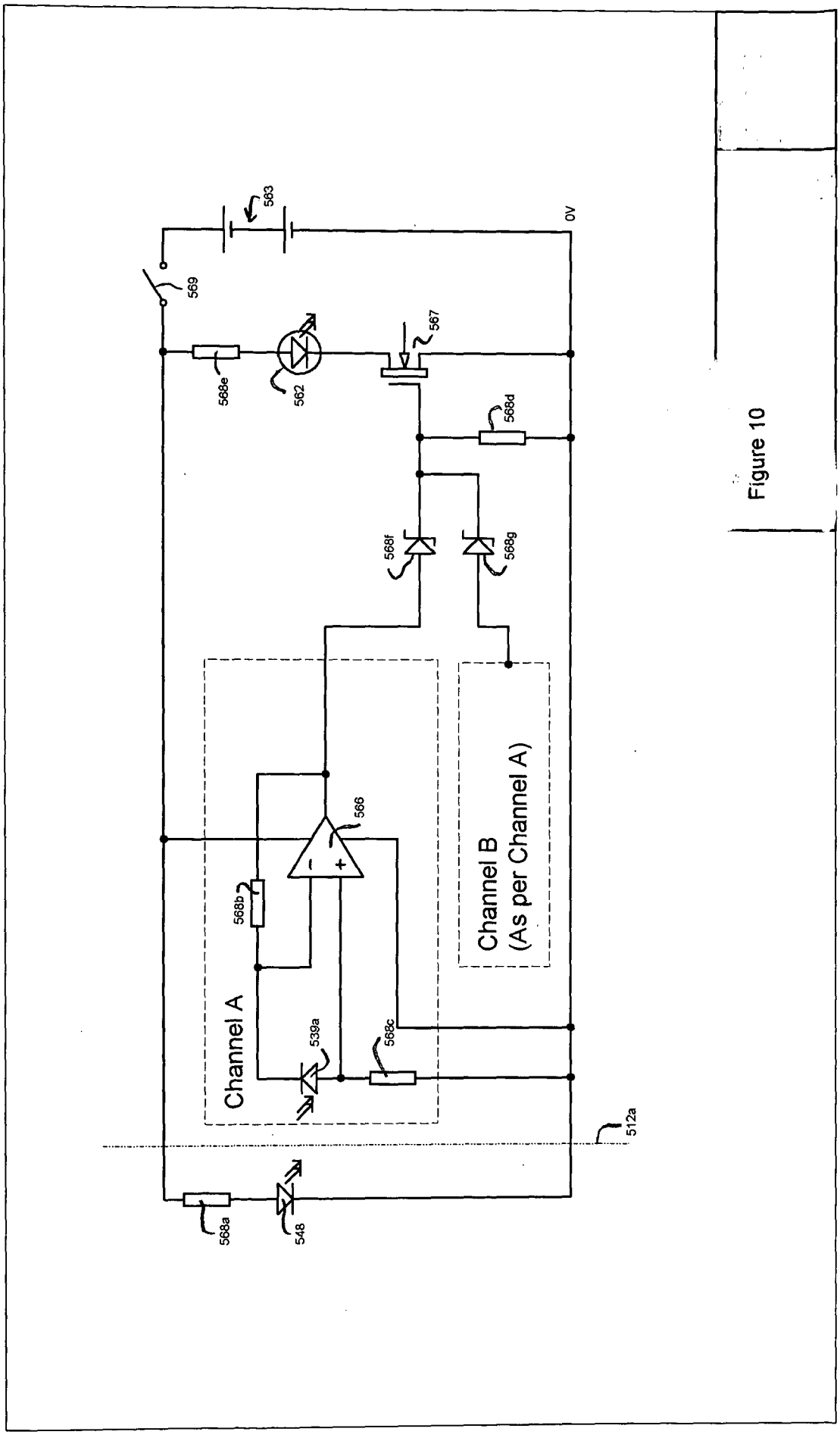

563
0V
569
567
562
568e
568d
568f
568g
566
568b
Channel A
Channel B
(As per Channel A)
539a
568c
512a
568a
548

Figure 10

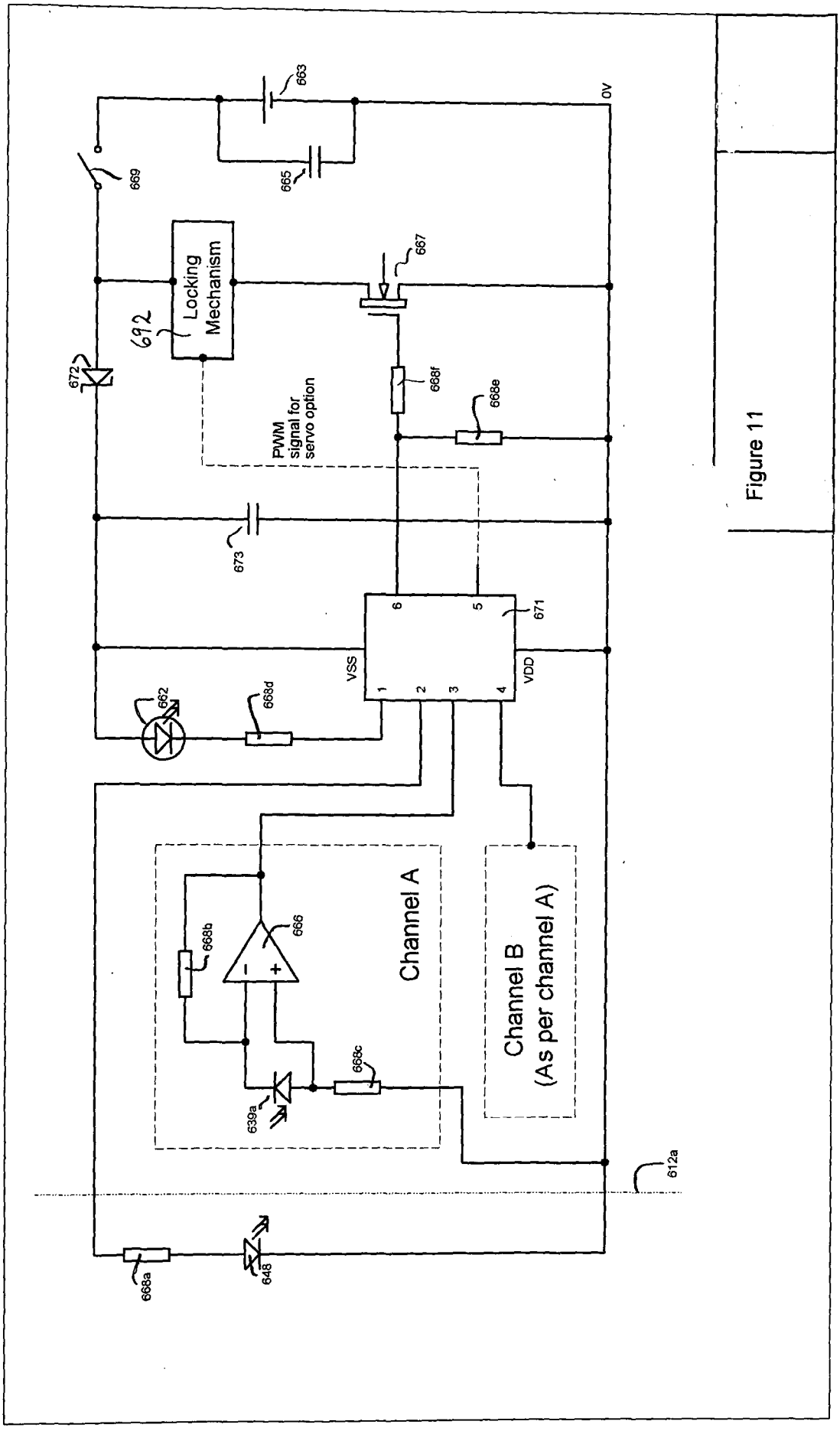

663
0V
669
665
Locking Mechanism
667
692
672
668f
668e
PWM signal for servo option
673
671
6
5
VSS
VDD
1
2
3
4
662
668d
Channel A
Channel B (As per channel A)
668b
666
668c
639a
612a
668a
648

Figure 11

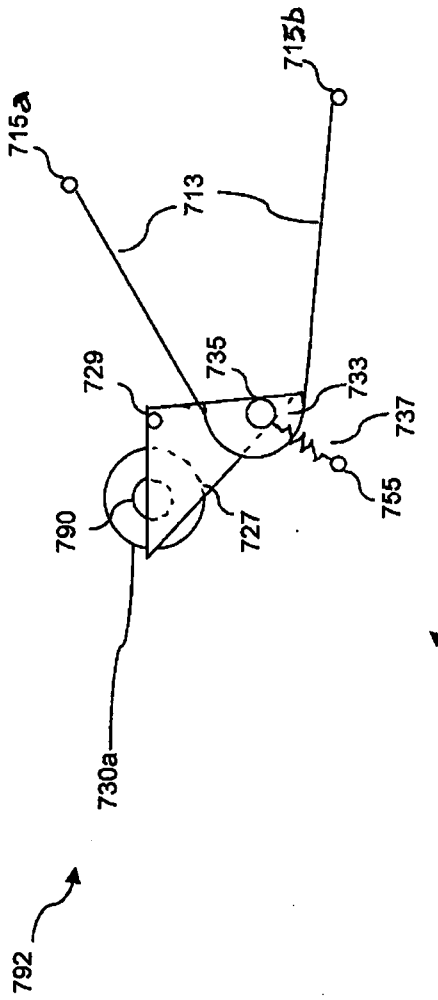


FIG. 12a

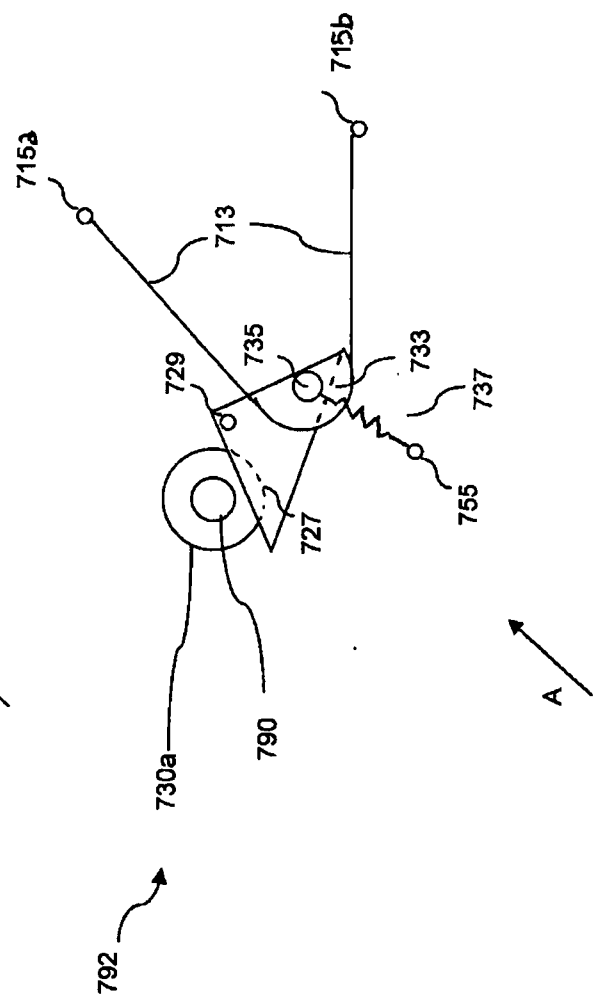


FIG. 12b

FIG. 13a

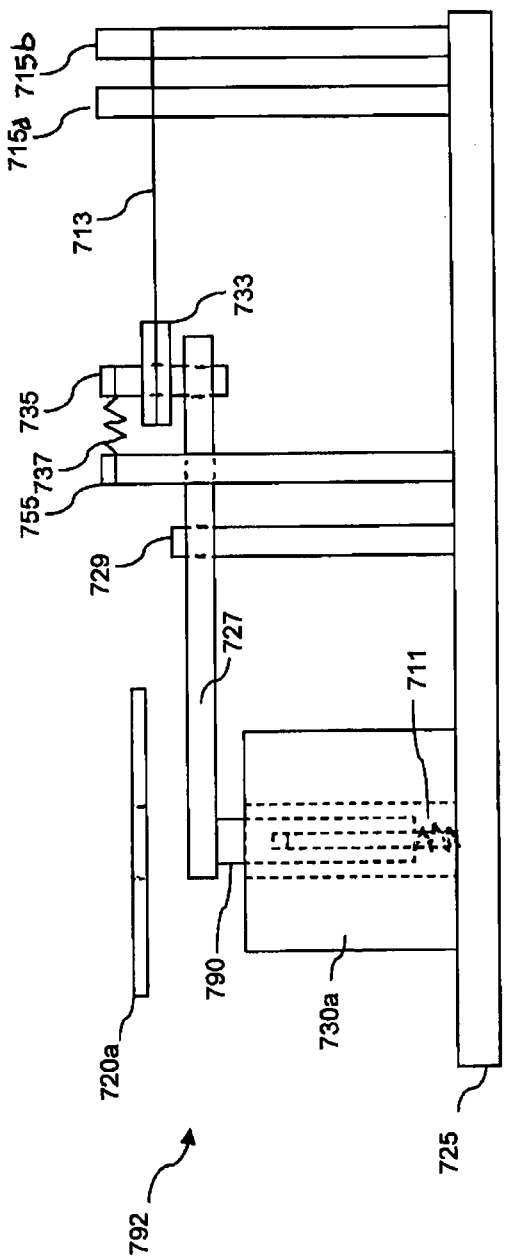


FIG. 13b

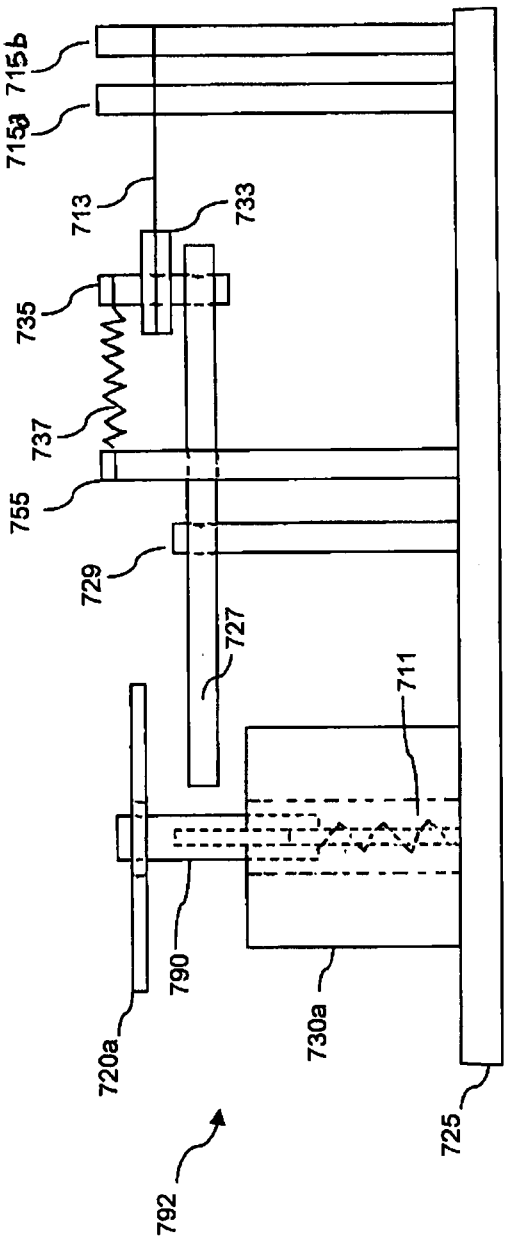


FIG. 14a

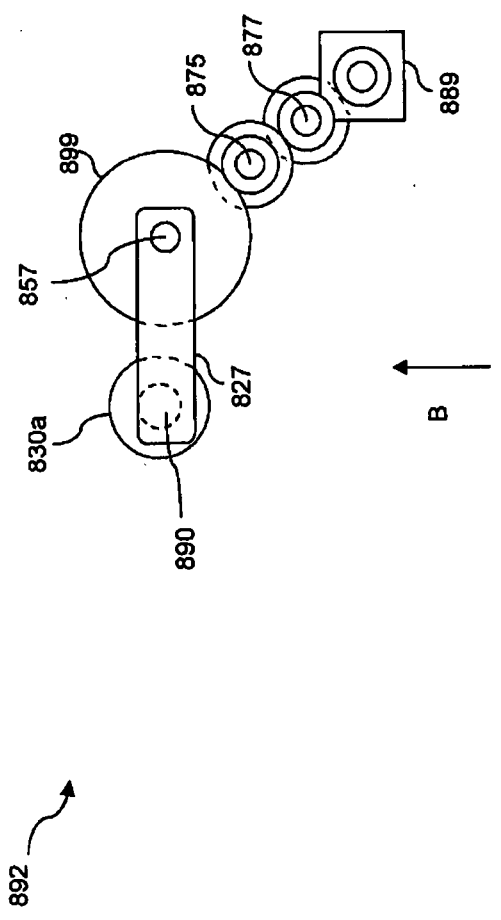
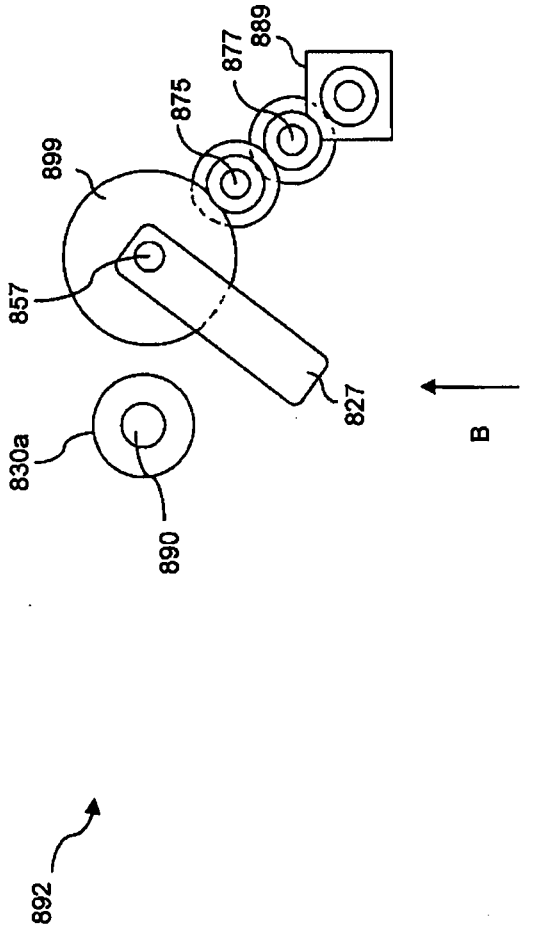


FIG. 14b



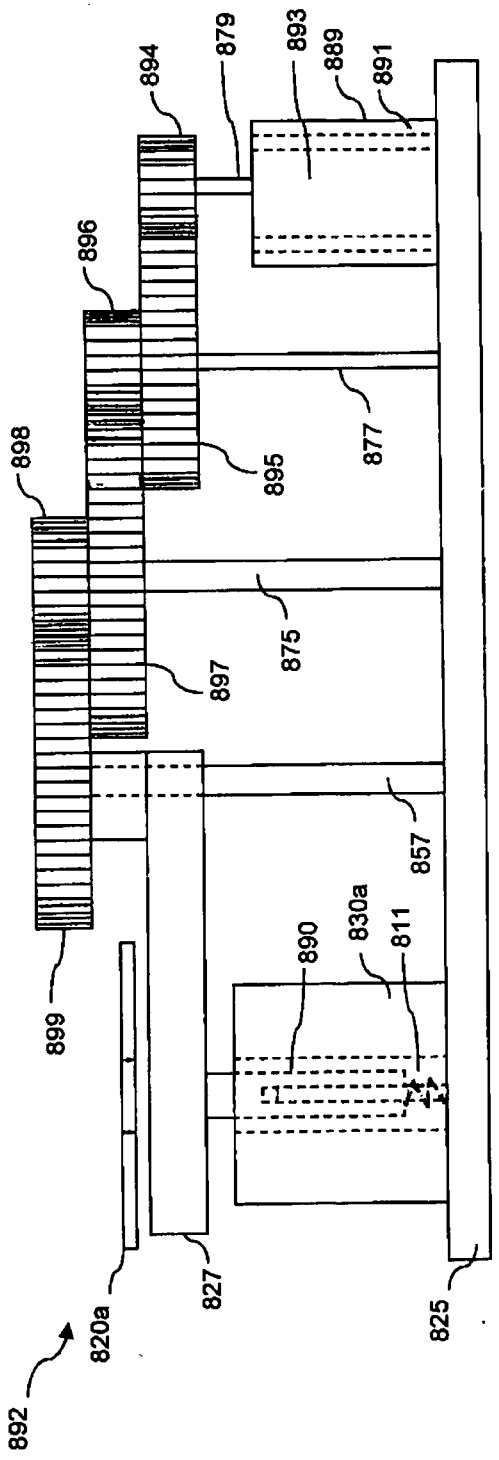


FIG. 15a

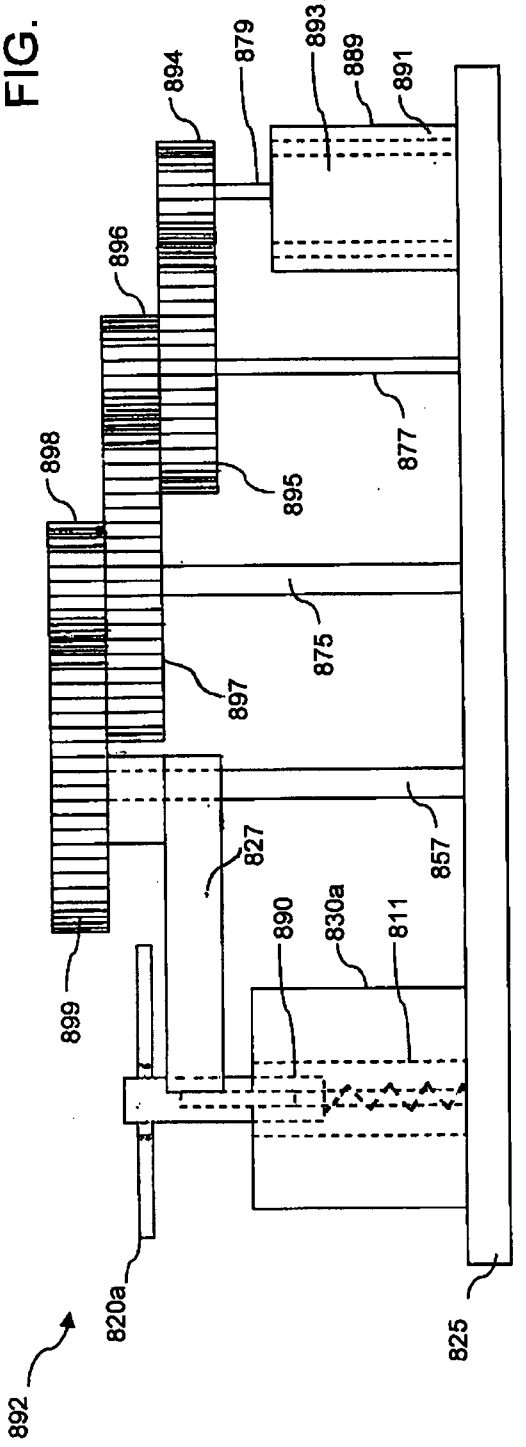


FIG. 15b

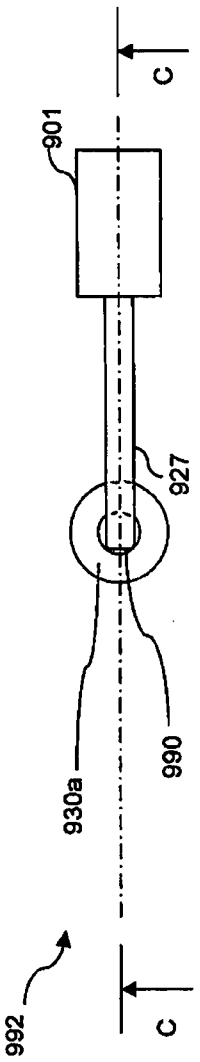


FIG. 16a

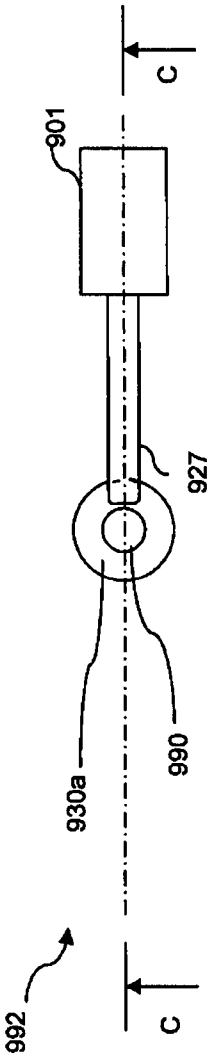


FIG. 16b

FIG. 17a

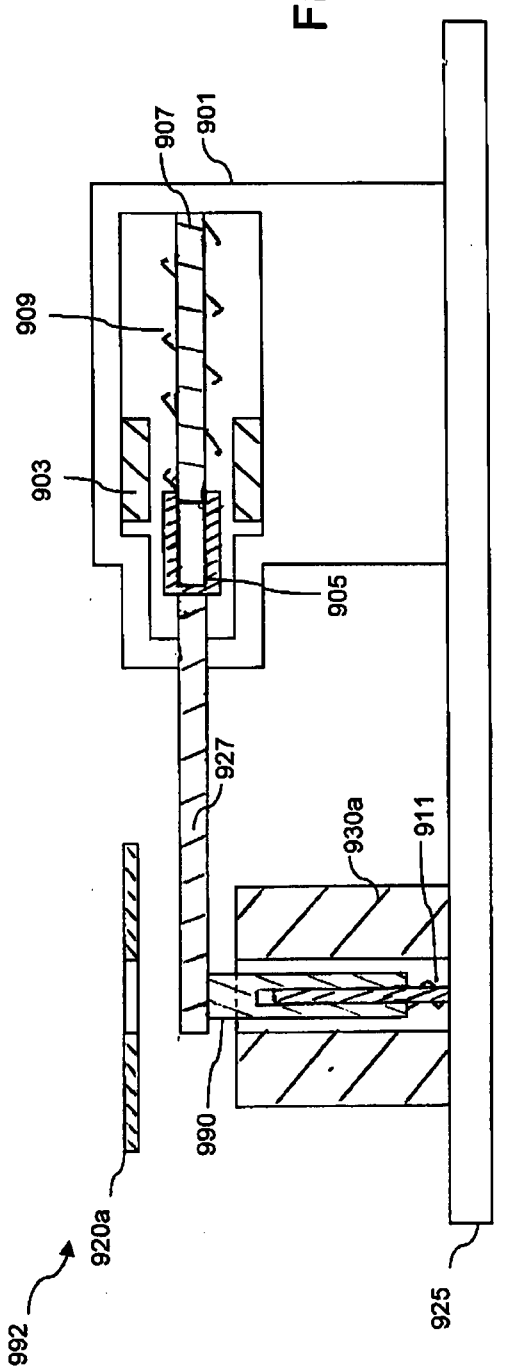


FIG. 17b

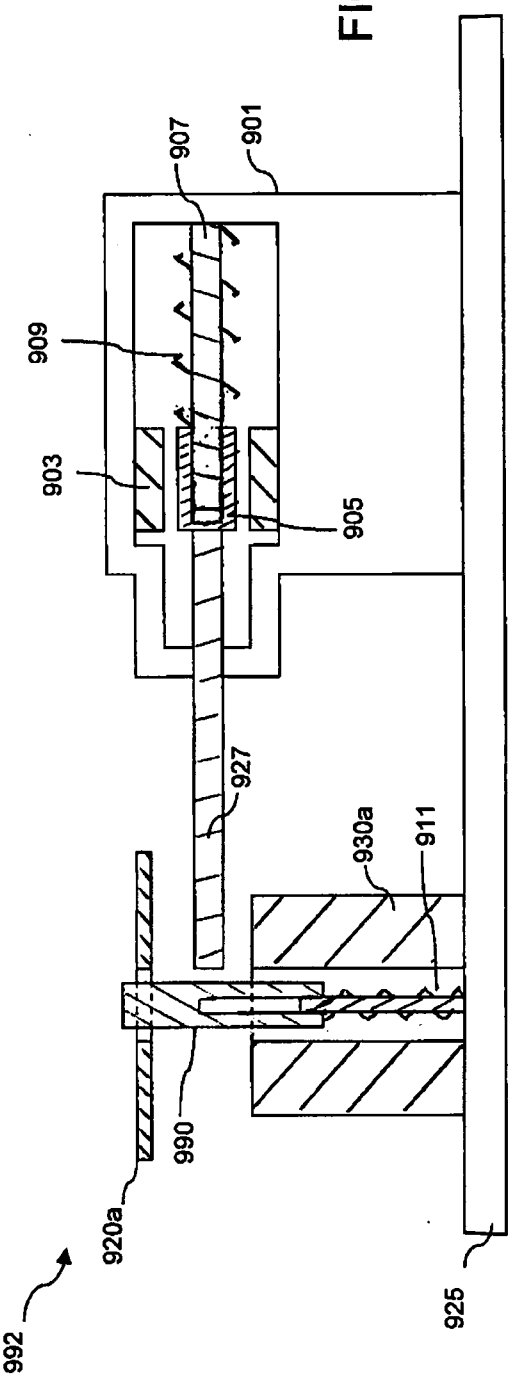


FIG. 18a

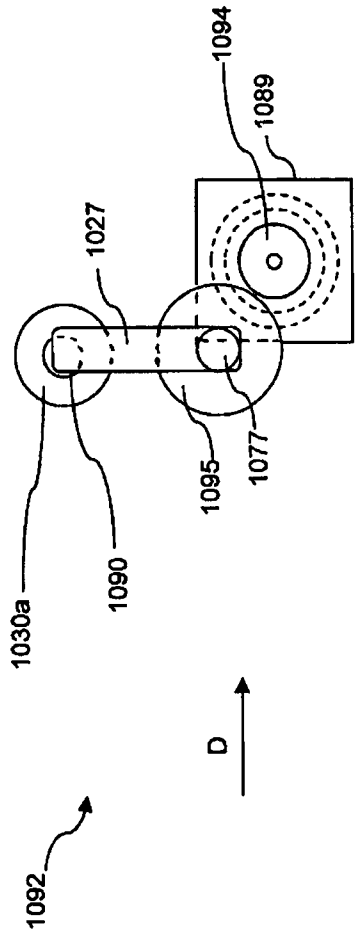
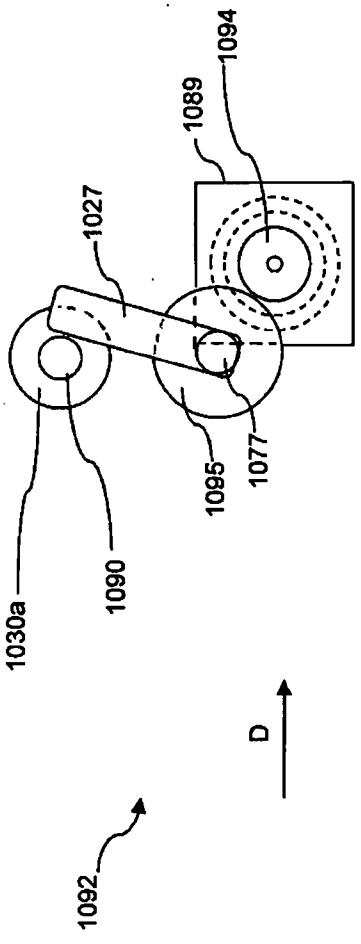


FIG. 18b



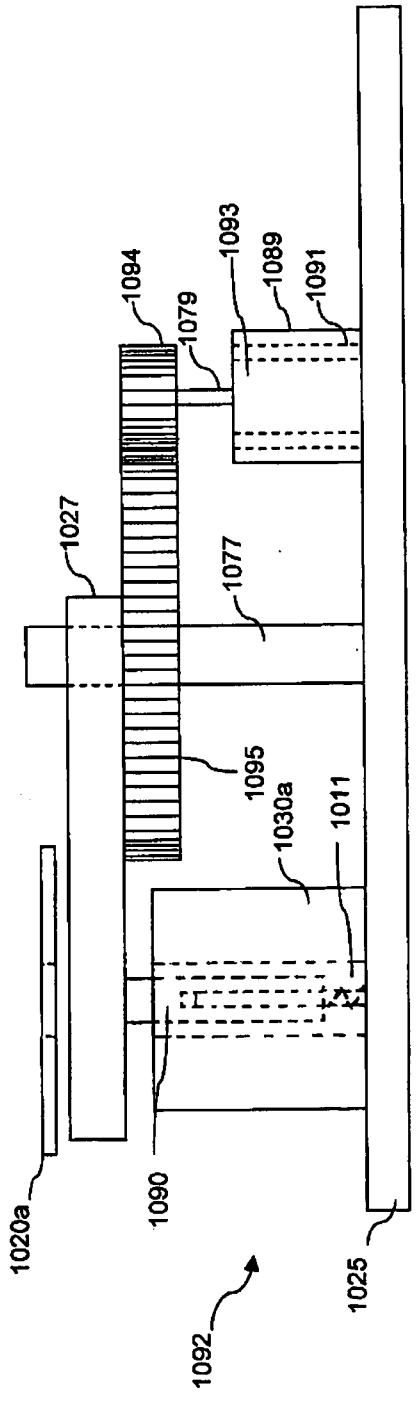


FIG. 19a

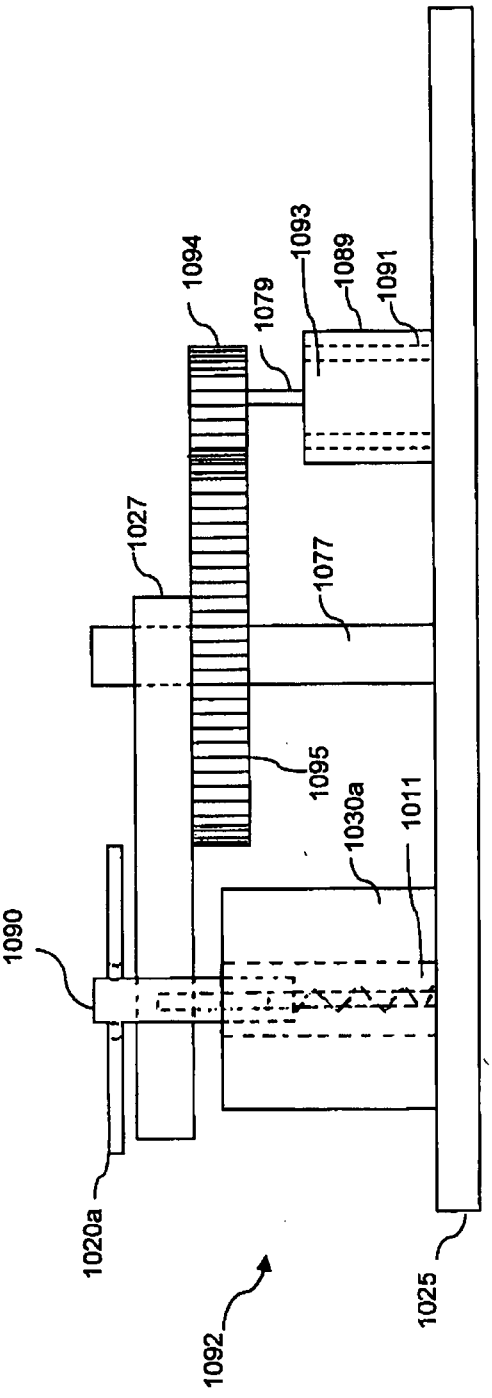


FIG. 19b

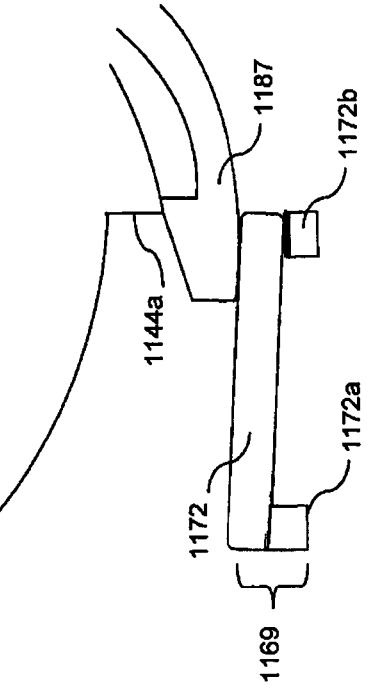


FIG. 20b

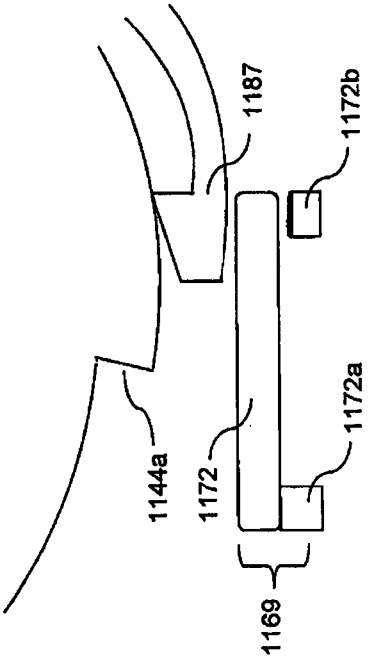


FIG. 20a

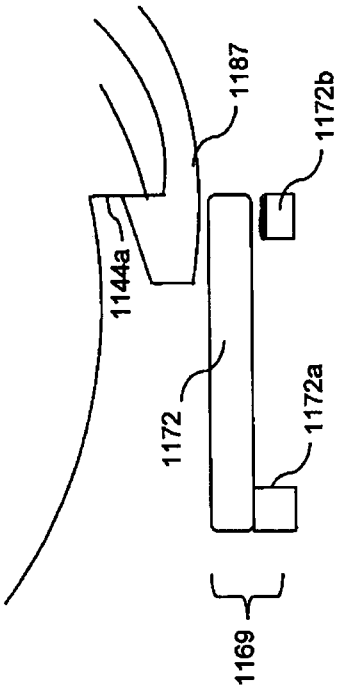


FIG. 20c

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/058406

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61M15/00

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 practical, 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	WO 2006/123110 A (GLAXO GROUP LTD [GB]; ANDERSON GREGOR JOHN MCLENNAN [GB]; HARVEY STEPH) 23 November 2006 (2006-11-23)	1,2, 11-18, 30,31, 46-53
A	page 30 - page 31; figure 28 page 2, line 10 - line 14	3-10, 32-45,54
A	WO 2007/038488 A (GLAXO GROUP LTD [GB]; ALCAN TECH & MAN LTD [CH]; SMITHKLINE BEECHAM CO) 5 April 2007 (2007-04-05) abstract	1
P,A	WO 2008/058964 A (GLAXO GROUP LTD [GB]; DAVIES MICHAEL BIRSHA [GB]; TANSLEY ROBERT WILLI) 22 May 2008 (2008-05-22) page 32; figure 3c	1

☐ 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 document 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
10 October 2008	15/12/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Valfort, Cyril

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2008/058406

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-20, 30-54

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-20,30-54

   A medicament dispenser with a fault detector comprising a sensor associated with a second path, said sensor being capable of detecting an absence of a metallic layer in said second path and being adapted to produce an output signal based on said detected absence

   ---

2. claims: Claims 21-29

   A medicament dispenser with a locking mechanism being adapted to move in response to an electrical drive input from a non-locking position to a locking position in the event that said fault condition is detected

   ---

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2008/058406

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006123110 A	23-11-2006	EP 1896101 A1	12-03-2008
WO 2007038488 A	05-04-2007	AR 058467 A1	06-02-2008
		AU 2006294788 A1	05-04-2007
		CA 2623586 A1	05-04-2007
		EP 1767347 A1	28-03-2007
		US 2008251411 A1	16-10-2008
WO 2008058964 A	22-05-2008	NONE	