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A DEVICE FOR DISPENSING AND SPREADING A LIQUID

This application claims the benefit U.S. Provisional Application No. 61/909,298, filed on November 26, 2013, the contents of which are hereby incorporated by
5 reference in their entirety into the present disclosure.

This invention relates to a device for dispensing and applying a volume of liquid to a treatment surface. In further embodiments the invention relates to a system for administration of a physiologically active agent and a method of transdermal administration using the device. The device is particularly, but not
10 exclusively, suited for the application of a metered volume of transdermal composition containing testosterone to a skin surface of a user. The invention also provides a method of transdermal administration of a pharmaceutically active, particularly testosterone, using the device. It will be convenient to hereinafter describe the invention with reference to this preferred application;
15 however, it is to be understood that the invention is not limited to this preferred application.

For the purpose of this specification the term liquid is intended to include all forms of liquids, lotions, gels, and creams.

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It is generally understood that in order for a pharmaceutical, medicinal or therapeutic liquid (hereinafter liquid) to achieve a desired efficacy, it needs to be applied in accordance with the manufacturer's directions. This is particularly the case where the liquid is a medicated liquid intended to have a therapeutic effect
25 at a certain dose of the active ingredient. Often in such cases, a specific volume of liquid will need to be applied to achieve the desired efficacy. If more than the specified volume of liquid is applied the user may suffer an adverse reaction, whereas if less than the specified volume of liquid is applied the desired efficacy may not be achieved.

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Topical or transdermal liquids have previously been provided in squeezable containers or in containers with a finger operated pump. Such containers

provide the user with a number of problems. For instance, it is very difficult for a user to dispense an accurate or measured volume from a squeeze container. Furthermore a finger operated pump requires the user to be capable of completing the stroke of the pump in order to accurately dispense the specified
5 volume of liquid. In cases where the user makes an incomplete stroke, or multiple incomplete strokes, the pump may not dispense the required volume. Furthermore where a finger operated pump is supplied, inadvertent operation of the pump, while not in use can result in undesirable leakage of liquid. In either
10 case of the squeeze container or pump, it can be difficult for the user to control the liquid as it is dispensed. A dispenser that facilitates dispensing the correct volume of liquid where a specified volume of liquid is required, and prevents leakage when not in use, would be desirable.

The manufacturer's directions often specify that the liquid should be dispensed
15 into the palm of the user's hand for subsequent transfer to the treatment surface. In situations where the liquid is dispensed directly onto the treatment surface the liquid is often spread over the treatment surface using the palm of the hand, the fingers, the wrist or the forearm. This can result in residual liquid remaining on the user's hand(s) or arm(s) which is not ideal. Furthermore, this
20 residual liquid can result in transference of the liquid via direct or indirect contact with objects, other people, and animals. This can result in persons other than the user receiving treatment that they do not require, resulting in potentially harmful side effects with certain actives. It is generally desirable to limit application of the liquid to the treatment surface of the user only.

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Devices have been designed to deposit topical liquids on the skin which do not require spreading or contact with the free hand. Some such devices dispense the liquid onto an applicator that is then used to spread the liquid over the treatment surface. This system of application suffers from the fact that the
30 user has to physically transfer the liquid from the dispenser to the applicator before applying the liquid to the skin. Such a system is susceptible to a risk that the liquid will project from the pump or squeeze bottle, miss, or splash from, the applicator, and land on the hand or body parts of the user.

Another type of dispenser system that is used to apply a topical liquid to the skin, that does not involve a user initiated physical transfer of the liquid from the dispenser to the applicator, is a roll-a-ball type system that is often used for applying anti-perspirants and deodorants to the axilla area of the body. The roll-a-ball is brought into contact with a bulk storage of the liquid which is transferred to the treatment surface of the user by rolling the ball across the treatment surface. This reduces the likelihood that liquid will be applied to, or reside on, parts of the body that are not intended to be treated. This type of applicator is not entirely satisfactory for medicated liquids as it is difficult to control the volume of liquid being applied.

Another issue with certain devices is inadvertent dispensing of the liquid by way of unintended operation of the pump. This can result in wasted liquid or even indirect transference if the liquid is dispensed over objects, unintended body parts, or animals which subsequently come into contact with other persons. Alternatively the pump may be operated by an unauthorised person, such as a child, which can lead to inappropriate dosing. It is generally desirable to try to limit use of the pump to intended and authorised use only.

A reference herein to a patent document or other matter which is given as prior art is not to be taken as an admission that that document or matter was known or that the information it contains was part of the common general knowledge as at the priority date of any of the claims.

According to one aspect of this invention there is provided a device for dispensing and applying a volume of liquid to a treatment surface, the device having an axis and including, a container for containing the liquid, a pump for extracting the volume of liquid from the container, an actuator for operating the pump, a receptacle defining a reservoir space while accommodating the extracted volume of liquid which substantially collapses when the volume of liquid is applied to the treatment surface, the receptacle having an aperture formed in a floor thereof through which the volume of liquid enters the reservoir space.

The receptacle may include a wall surrounding the floor, at least the wall of the receptacle is resiliently deformable so that in an erect condition it defines at least in part the reservoir space and resiliently deforms when the receptacle collapses. The floor and wall may be formed from a thin membrane. The pump
5 may include a head and a body with the head being movable in the direction of the axis so as to induce the volume of liquid to be expelled out of the head of the pump, the floor of the receptacle being resiliently deformable and operatively associated with the pump head so as to deform when the head is moved. The head may be movable towards the body when inducing the volume
10 of liquid to be expelled out of the head of the pump. The reservoir space has a depth, and it is preferred that the floor of the receptacle is movable with the pump head so that the depth of the reservoir space increases when the head is moved towards the body. This preferred arrangement reduces the likelihood that the liquid will inadvertently egress from the reservoir space while the pump
15 dispenses the liquid.

The device preferably includes a diffuser which diffuses the liquid as it enters the reservoir space. The diffuser may take any suitable form and one form may include a single inlet and multiple outlets to guide the liquid across the floor of
20 the reservoir space. It is preferred that the outlets are oriented relative to the inlet so as to cause the liquid to change direction as it travels from the inlet to the outlets. These preferred features further control the dispensing of liquid from the pump, reducing the likelihood that the liquid will inadvertently egress from the reservoir space.

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The actuator may include a base which is fixed relative to the container, a rotatable member that is rotatable relative to the base, and a shuttle that operatively interacts with the pump, and rotates with the rotatable member, and moves relative to the base in the axial direction when the pump extracts the
30 volume of liquid. The device may include a rack and pawl mechanism associated with the rotatable member and the base configured to hinder the rotation of the rotatable member in a non-preferred direction. It is preferred that the rack and pawl mechanism is configured to cause a greater level of hindrance to rotation of the rotatable member in the non-preferred direction

when the actuator is in a rest position. This may be achieved in any suitable manner which may include the rack including a plurality of teeth of one size and one tooth that has a larger trailing edge, wherein the interaction of the pawl with the larger trailing edge causes said greater level of hindrance. The larger trailing edge is preferably at least 40% greater in depth than a trailing edge of a majority of the teeth.

The actuator may include a cam means so that rotation of the rotatable member causes axial movement of the shuttle from a first position toward a second position. The cam means may include a cam surface on the shuttle and a cam follower on the base, wherein the cam follower moves along the cam surface on rotation of the rotatable member. It is preferred that the cam surface is configured to interact with the follower so as to reduce resistance on the shuttle returning to the first position as the actuator approaches a rest position. This may be achieved in any suitable manner and one arrangement may include the cam surface is shaped with an end portion which is aligned substantially vertically so as to permit the shuttle to return to the first position before the actuator reaches the rest position. This preferred arrangement reduces the resistance on the head of the pump returning to a closed position.

The shuttle and rotatable member may include guide means to limit movement of the shuttle relative to the rotatable member to movement in the axial direction. The device may include a stop means for preventing the shuttle from moving in the axial direction unless by way of rotation of the rotatable member.

The pump is preferably a positive displacement pump and the container includes a relatively rigid outer shell and a relatively collapsible inner lining, whereby the liquid is retained in the lining which collapses upon operation of the pump.

According to another aspect of this invention there is provided a device for dispensing and applying a volume of liquid to a treatment surface, the device including: a container for containing the liquid, a pump for extracting the volume of liquid from the container, an actuator for operating the pump, a receptacle

defining a reservoir space for accommodating the extracted volume of liquid, the receptacle is used to apply the liquid to the treatment surface, a cap that covers the receptacle and prevents operation of the actuator when in a closed position and, when in an open position reveals the receptacle and permits
5 operation of the actuator, a latch that interacts with the cap so that in a latch condition retains the cap in the closed position and can be adjusted to a release condition to allow the cap to be moved to the open position.

The device may include a base that is fixed relative to the container which
10 includes the latch, whereby the base is configured to resiliently deform to adjust the condition of the latch between a latch condition and a release condition. The latch may include a pair of tabs on opposed sides of the base, and the base includes a deformation zone adjacent each tab which is resiliently deformable for adjusting the condition of the latch. The cap may include a pair of apertures
15 formed adjacent an open end of the cap at opposed sides thereof, whereby each aperture receives one of the tabs when the cap is in the closed position and the latch is in the latch condition. The base may include a seat zone for accommodating the open end of the cap, the seat zone being sized to accommodate the open end of the cap in a friction fit. The seat zone includes
20 an annular wall which engages an inner surface of the cap adjacent the open end, the inner surface overlapping with the annular wall so as to produce the friction fit. The inner surface of the cap may overlap with the annular wall so as to prevent tilting of the cap relative to the base. The inner surface of the cap may overlap with the annular wall so as to require the cap to be moved in an
25 axial direction when moving to the open position. It is further preferred that both deformation zones be depressed to move the cap to the open position. This preferred aspect reduces the likelihood that the cap will be inadvertently removed from the base, and in particular removed by a child. It is still further preferred that the actuator includes a rotatable member that rotates relative to
30 the base to operate the pump, wherein the cap prevents rotation of the rotatable device when the cap is in the closed position. This preferred arrangement reduces the likelihood that the pump will be inadvertently operated.

The receptacle may be resiliently deformable so as to collapse when applying the liquid to the treatment surface and deforms when the actuator is operated.

5 The treatment surface may be any suitable area however it is preferred that the area is an axilla area of a user's skin.

10 The container may contain any suitable liquid and one preferred liquid is in the form of a composition including a physiologically active agent. It is further preferred that the physiological active agent is testosterone.

15 According to another aspect of this invention there is provided a device for dispensing and applying a volume of liquid to a treatment surface, the device having an axis and including: a container for containing the liquid, a pump for extracting the volume of liquid from the container, an actuator for operating the pump, a receptacle defining a reservoir space while accommodating the extracted volume of liquid which substantially collapses when the volume of liquid is applied to the treatment surface, the receptacle having an aperture formed in a floor thereof through which the volume of liquid enters the reservoir space, wherein the reservoir space has a depth, and the floor of the receptacle is movable with operation of the pump head so that the depth of the reservoir space increases while the liquid enters the reservoir space.

20 According to a further aspect there is provided a system for transdermal administration of testosterone from a liquid the system comprising a device as herein before described, wherein the container contains a liquid composition comprising testosterone.

30 According to a further aspect there is provided a method of transdermal administration of a physiologically active agent to a subject including providing a device as herein described wherein a liquid comprising the pharmaceutically active agent is contained in the container; pumping a volume of liquid from the container through the aperture formed in a the receptacle to the receptacle defining a reservoir space to accommodate the extracted volume of liquid, wherein the reservoir space is adapted to substantially collapse when the

volume of liquid is applied to the treatment surface; and spreading the liquid over an area of skin in at least one axilla of the subject.

According to a further aspect there is provided a method of dispensing a volume of liquid for application to a skin surface including: providing a device as herein described comprising a container containing the liquid, pumping a volume of liquid from the container through the aperture formed in a the receptacle to the receptacle defining a reservoir space to accommodate the extracted volume of liquid wherein the reservoir space is adapted to substantially collapse when the volume of liquid is applied to the treatment surface.

According to a further aspect there is provided a method of increasing the testosterone blood level of a person in need thereof comprising applying to at least one axilla of the person a liquid comprising testosterone wherein the liquid is applied by a device as herein described and the liquid comprises:

- (a) testosterone in an amount of from 0.01 % to 10 % w/v of the liquid composition;
- (b) ethanol, isopropanol or mixture thereof in a total amount of from 10 % v/v to 99 % v/v of the liquid composition;
- (c) octyl salicylate in an amount of from 0.01 % to 15 % w/v of the liquid composition; and
- (d) optionally a thickening agent.

It will be convenient to hereinafter describe the invention in greater detail by reference to the attached illustrations which show a preferred embodiment of the various aspects of this invention. The particularity of those drawings and the related detailed description is not to be understood as superseding the generality of the proceeding description of the invention according to each of its aspects.

In order that the invention may be more fully understood, some embodiments will now be described with reference to the figures in which:

Brief Description of the Drawings

Figure 1 is an isometric view of a preferred embodiment of the device according to one aspect of the invention.

- 5 Figure 2 is an exploded view of the preferred embodiment from Figure 1.

Figure 3 is a reverse exploded view of the embodiment from Figure 2.

- 10 Figure 3a is a schematic detail of the teeth of the rack from figure 3 with the collar in a rest position.

Figure 4 is a cross sectional view of a portion of the device with the cap in a closed position and a latch in a latched condition.

- 15 Figure 5 is the preferred embodiment from Figure 4 with the latch in the release condition.

Figure 6 is a sectional isometric view of a portion of the device with the cap detached

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Figure 7 is a cross sectional view of a portion of the device with the actuator in a rest condition.

- 25 Figure 7a is a schematic elevation view of the shuttle and follower corresponding to the position illustrated in figure 7.

Figure 8 is a cross sectional view of the device with the actuator rotated through 90° relative to the base.

- 30 Figure 8a is a schematic elevation view of the shuttle and follower corresponding to the position illustrated in figure 8.

Figure 9 is a front elevation view of the device in use.

Figure 9a is a schematic elevation view of the shuttle and follower as the collar approaches the rest position.

Detailed Description of the Drawings

- 5 Figure 1 illustrates a preferred embodiment of the device 1 according one aspect of the invention. The device 1 includes a cap 2 which is shown in a detached position, a container 3, an actuator 4 in a rest position and an empty receptacle 5. The device 1 is designed for dispensing a volume of liquid to the receptacle 5, and using the receptacle 5 to spread the liquid over a treatment
- 10 surface 6 (see Figure 9). The receptacle 5 may take any shape in order to receive and spread the liquid and the invention is not limited to a receptacle 5 of the shape as illustrated in figure 1. The treatment surface 6 may be any surface designated by the user and this includes a skin surface of the user. The device 1 is particularly suited to apply liquid to an axilla area of the user's skin,
- 15 however the invention is not limited to application in this area only. It is preferred that the reservoir space 10 be within a range of 2ml to 20ml, with approximately 5ml being most preferred when the liquid dispensed contains a drug.
- 20 Figure 1 illustrates a preferred form of actuator 4 including a rotatable collar 7 and a base 8. The base 8 is fixed in position relative to the container 3 whereas the collar 7 is rotatable (in the direction of the arrow) relative to the base 8 about the axis X-X shown in Fig. 1. This rotation causes operation of the pump 9 (see Figure 2). The pump 9 forces liquid out of the container 3 and into a reservoir
- 25 space 10 defined by the receptacle 5. Figure 1 also illustrates a preferred form of part of a latch 11 which interacts between the cap 2 and the base 8 to retain the cap 2 in a closed position (see Figure 4). The other features of the actuator 4 will be described in greater detail by reference to the later illustrations. The function of the actuator 4 is to facilitate operation of the pump 9. It should be
- 30 appreciated that the actuator 4 may take any suitable form and the invention is not limited to the form described in this detailed description and illustrated in the attached figures.

The container 3 may take any shape and is not limited to the shape of a bottle as illustrated in the figures. Furthermore the container 3 may directly contain the liquid, or indirectly containing the liquid, by for example way of a bag (not shown) of liquid within the container. Where the device 1 is applying a drug in liquid form, it is desirable for the liquid to be contained within a bag. The bag may reduce in volume as the liquid is dispensed to reduce the likelihood of the air spoiling the drug. While part of the function of the container 3 is to contain, directly or indirectly, the liquid, another function of the container 3 is to provide a handle for the user to grip while operating the actuator 4.

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Referring now to Figure 2 which illustrates the base 8 spaced from the container 3, the base 8 preferably snap fits onto the container 3 by interaction of annular projecting portions 12 of the base 8 with annular projecting portions 13 of the container 3 (see Figure 4). The snap fit is preferably designed to allow for easy assembly of the device 1, while providing a relatively permanent connection between the base 8 and the container 3. The annular projecting portion 13 of the container 3 also includes a pair of opposed locating lugs 14 (see Figure 2), which locate in slots 15 (see Figure 3) formed in the annular projecting portion 12 of the base 8. The lug 14 and slot 15 arrangement helps locate the base 8 on the container 3 while preventing rotation of the base 8 relative to the container 3. It should be appreciated that the location of the lugs 14 and slots 15 could be reversed while still achieving the same function. Furthermore the location of the lugs 14 and the slots 15 on the base 8 and container 3 respectively may vary from the positions as shown in the illustrations.

25

The pump 9 illustrated in Figure 2 includes a pump head 16 and the pump body 17. The pump head 16 is often referred to in the industry as a pump stem and for the purposes of this specification the terms pump head and pump stem are interchangeable. A spring 53 (see Figure 5) acts between the head 16 and the body 17 to urge the head 16 away from the body 17. Movement of the head 16 towards the body 17 causes operation of the pump 9 by pressurising the liquid contained within the container 3, forcing a metered quantity of the liquid into a pump chamber 54 (see Figure 5) and out through an outlet 19 in the head 16 of the pump 9. Thereafter the spring 53 returns the head 16 to the rest position to

re-fill the pump chamber 54 with liquid from the container 3. The action of returning the head 16 to the rest position also seals the pump head 16 which inhibits evaporation of liquid from the pump chamber 54, and leakage of liquid from the pump chamber 54 back into the container 3. This facilitates ensuring
5 the pump chamber 54 remains filled with the correct dose of liquid for when the pump 9 is next operated. The action of returning the head 16 back to the rest position is as a result of force applied by the spring 53. Whilst it is desirable for the force be sufficient to return the head 16 to the rest position, that force must not be too great to prevent a user from depressing the head 16.

10

The preferred form of pump 9 is a positive displacement pump as it is capable of providing a specified volume of liquid, however other forms of pump may also be suitable. The function of the pump 9 is to dispense liquid from the container and it is preferred that this be achieved in an accurate and repeatable manner.
15 Clearly other forms of pump may be suitable and the invention is not limited to the form of pump described in this detailed description and illustrated in the attached figures. Not all features of the pump body 17 are illustrated in the figures 4 to 8, as the invention is not to be limited to a pump having specific internal components. The internal components may vary to suit the needs of the
20 liquid to be dispensed.

Figure 2 also illustrates a shuttle 20 which forms part of the actuator 4, which in use is located within the collar 7. The shuttle 20 includes a pair of shoulders 21 on opposed sides thereof which locate in slots 22 formed in an inner wall 23 of
25 the collar 7. The shoulders 21 and slots 22 arrangement ensure the shuttle 20 rotates with the collar 7, while limiting relative movement between the shuttle 20 and collar 7 to movement in the axial direction that is along axis X-X. This axial movement is achieved by a cam surface 24 formed on the shuttle 20 interacting with a cam follower 25 formed on the inside surface of a neck portion 26 of the
30 base 8. Figure 2 illustrates the shuttle 20 having a pair of opposed cam surfaces 24 and the neck 26 having a pair of opposed cam followers 25 which is preferred to balance the forces acting on the shuttle 20. Rotation of the collar 7 causes rotation of the shuttle 20 about the axis X-X also, which causes the cam surface 24 to move over the cam follower 25. The cam surface 24 is ramped so

that rotation of the collar 7 through 90° from the rest position illustrated in Figure 1 moves the shuttle 20 completely down to fully depress the pump head 16 towards the pump body 17. This movement of the head 16 is against the force of the spring 53 and results in a dose of liquid being dispensed from the container to the receptacle. Continued rotation of the collar 7 through a further 90° moves the cam follower 25 over the cam surface 24 to allow return of the shuttle 20 to the rest position with the assistance of the spring 53. This results in the pump chamber 54 being refilled as previously described.

10 The collar 7 is preferably retained by the base 8 by snap fitting onto the base 8. The preferred embodiment illustrated in Figure 2 and 3 has a free end of a neck 26 of the base 8 including a lug formation 27 about the perimeter thereof. A ledge formation 28 (see Figure 2) on the inner surface of the collar 7 interacts with the lug formation 27 (see for example figure 4). The neck portion 26 of the
15 base 8 includes vertically extending notches 29 adjacent the free end so as to allow the perimeter of the free end to contract when fitting through an opening 30 (see Figure 3) in the collar 7. This allows the neck 26 to resiliently deform until such time as the lugs 27 locate over the ledge 28 formed in the collar 7 (see Figure 4).

20

It is generally desirable to control movement of the pump 9 head 16 relative to the body 17, so as to ensure the pump 9 dispenses the correct metered volume of liquid. This may be achieved by any suitable arrangement and in the embodiment illustrated rotation of the collar 7 is limited to one direction only.
25 More specifically, the device 1 is designed so as to inhibit rotation of the collar 7 against the direction of the arrow on the collar 7. Figure 2 illustrates the collar 7 being formed with the arrow on an outer surface thereof to indicate the direction of movement of the collar 7 relative to the base 8. It can be appreciated from Figure 3 that the collar 7 has a rack formation 31 around the opening 30. This
30 rack formation 31 interacts with a flexible detent or pawl 32 formed on the neck 26 of the base 8 so as to function as a ratchet. The detent or pawl 32 slides over the rack formation 31 as the collar 7 is rotated in the direction of the arrow. The pawl will lock into the rack formation 31 if attempts are made to rotate the collar 7 against the direction of the arrow. This prevents the collar 7 being

rotated back and forth to dispense more than the intended amount. Instead the user is limited to rotating the collar 7 in one direction only.

It is preferred that the rack formation 31 be configured to create a greater level
5 of hindrance to rotation of the collar 7 against the direction of the arrow when
the actuator is in a rest position. This may be achieved in any suitable manner
and in the embodiment illustrated the rack 31 has thickness T1 between the
majority of the teeth 48, and a thickness T2 at a location that the pawl 32 seats
10 48 with a larger trailing edge 52 that creates a greater barrier to the pawl 32 if
the collar 7 was to be rotated against the direction of the arrow from the rest
position. This trailing edge 52 may be up to 40% larger than the trailing edge of
the remainder of the teeth 48. Furthermore when the pawl 32 moves over the
larger trailing edge 52 it may also provide a tactile indicator to the user to
15 indicate the collar 7 has reached the rest position.

It can also be appreciated from figure 3a that there is clearance under the pawl
32 when located in the trough 49. This removes the load from the pawl 32 that it
experiences when traveling over the remainder of the teeth 48. This reduces the
20 likelihood of the pawl 32 from permanently deforming over time if it remained
under load, which is a particular issue when the pawl 32 (or whole base 8) is
formed from a plastics material referred to as plastic creep.

It is generally desirable that the shuttle 20 be prevented from operating the
25 pump 9 other than by way of rotation of the collar 7. In this regard Figure 3
illustrates the shuttle 20 being formed with a V-shaped formation 33 on an outer
surface thereof, with a corresponding formation on an opposed side of the
shuttle 20 (obscured). The V-shaped formation 33 is aligned to abut the cam
follower 25, if directly depressed, when the actuator 4 is in the rest position
30 shown in Figure 2. It ought to be appreciated that once the collar 7 is rotated
relative to the base 8, the V-shaped formation 33 is moved out of alignment with
the cam follower 25 so as to allow the shuttle 20 to depress the head 16 of the
pump 9.

Figure 2 also illustrates a floor portion 34 of the receptacle being formed with a centrally located aperture 35. The aperture 35 receives a shaft portion 36 of a diffuser 37 of the device 1. The shaft portion 36 also extends through a central bore 38 in the upper surface of the shuttle 20 to locate within the outlet 19 of the pump 9 (see Figure 4). This attaches a central zone of the floor portion 34 of the receptacle 5 to the shuttle 22, so that at least the floor portion 34 of the receptacle 5 moves with the shuttle 20 in the axial direction along axis X-X when the collar 7 is rotated. This movement of the floor portion 34 of the receptacle 5 will be described in greater detail with reference to latter illustrations.

Figure 4 illustrates a portion of the device 1 in cross section with the cap 2 in a closed position. The latches 11 on opposed sides of the base 8 are shown in the latch condition. The latches 11 include tabs 39 illustrated located in opposed apertures 40 (see Figure 3) formed adjacent the open end of the cap 2. When comparing Figure 4 with Figure 5, it can be appreciated that each of the tabs 39 have been moved out of the apertures 40 formed on opposed side of the cap 2. The latch is considered to be in a release condition when the tabs 39 are moved out of the apertures 40. This allows the cap 2 to be moved axially towards the open position as shown in Figure 1. The movement of the tabs 39 is achieved by the user simultaneously applying pressure on deformation zones 41 of each latch. The tolerance between the cap 2 and the base 8 is such as to require simultaneous pressure on the deformation zones 41 to allow the tabs 39 to disengage from the apertures 40. More specifically movement of either tab 39 only will not permit removal of the cap 2 from the base 8. Furthermore the latches are formed so as to require a force of in the range of 20N to 40N acting on both depression zones before the latches 11 will release. Finally the location of the latches 11 on opposed sides of the base 8 is merely preferred for safety reasons, however the latches 11 may be located elsewhere on the base. These features have been considered within the capacity of the likely adult user population, while inhibiting use of the device 1 by children.

Once the pressure is released from the deformation zones 41, the resilient nature of the material forming the deformation zone 41 allows the tabs 39 to return to the positions illustrated in Figure 4. Once the device 1 has been used by the user, the cap 2 can be returned to the closed position by moving it down in the axial direction to snap lock over the tabs 39 of the latch 40.

Referring now to Figure 6, it can be appreciated that an outer rim 42 of the receptacle 5 is located in a recess 43 formed in an upper surface of the collar 7. Furthermore, the floor portion 34 of the receptacle 5 is seated on an upper surface of the shuttle 20 and attached thereto by the diffuser element 37. The shaft of the diffuser element 37 extends through the receptacle 5 and engages the outlet 19 of the pump 9 in a snap fit. The diffuser 37 defines a conduit 44 to allow the egress of liquid from the pump 9 outlet 19 to spread over the floor 45 of the receptacle 5. The conduit 44 is initially formed by a single passageway 45 extending in the axial direction towards the top of the diffuser 37. The conduit 44 changes from the single axial passageway 45 to multiple passageways 46 that extend in a radial direction, substantially parallel to the floor 34 of the receptacle 5. The change from a single passageway 45 to multiple passageways 46, and change in direction of the conduit 44 is designed to reduce the speed of the liquid exiting the diffuser 37 and reduce the likelihood of spillage from the receptacle 5.

It can be appreciated by comparing Figures 7 and 8 that when the shuttle 20 is depressed as illustrated in Figure 8, it draws the floor 34 of the receptacle 5 down to increase a depth of the reservoir space 10 from the upper rim 42. Also the wall 47 extending between the floor 34 and the rim 42 changes shape. A radius of curvature of an upper portion of the wall 47 is reduced and the length of the wall 47 stretched so as to increase the volume of the reservoir space 10. The receptacle 5 is of an oval shape and it is preferred that the wall thickness 47 vary so that the change in shape of the receptacle 5 is uniform. It is during this time that the liquid is dispensed out through the diffuser 37 into a relatively deep reservoir space 10. The deep reservoir space 10 in conjunction with the uniform deformation of the receptacle reduces the likelihood of spillage of liquid over the wall 47 of the receptacle 5. Upward movement of the shuttle resulting

from further rotation of the collar 7 returns the floor 34 of the receptacle 5 back to the position as illustrated in Figure 7 preparing the device 1 for application of the liquid to the treatment surface 6.

5 The application of the liquid from the reservoir space 10 onto the treatment surface 6 is illustrated in Figure 9. It is to be appreciated from this figure that the receptacle 5 is collapsible under the pressure of forcing the receptacle 5 onto the treatment surface 6. This reduces the overall depth of the reservoir space 10 and facilitates effective transfer of all the liquid from the receptacle 5 to the treatment surface 6. The collapse of the receptacle 5 is significant to the extent that it is substantially incapable of retaining liquid in the reservoir space 10 thereafter. Furthermore, the flexible nature of the receptacle 5 enhances the ability of the device 1 to spread the liquid over the treatment surface 6, and reduces the likelihood that liquid will remain in the reservoir space 10 after spreading.

The receptacle 5 may be formed from any suitable material provided that that material is resiliently deformable and liquid impervious. One preferred form of material is silicone. However, it may also be formed from a natural or synthetic rubber or coated polymer materials. It can be appreciated from at least Figure 8 that the receptacle 5 is preferably formed with a relatively thin membrane forming the floor 34 and wall 47 of the receptacle 5. The receptacle 5 may be formed in any suitable manner, however it is preferred it is formed by molding.

25 The cam surface 24 is preferably configured to interact with the follower 25 so as to reduce resistance on the shuttle 20 as the actuator 4 approaches the rest position. Figure 7 illustrates the actuator 4 in the rest position while figure 7a illustrates schematically the interaction of the cam surface 24 with the follower 25 (with the base 8 not shown for clarity). The shuttle 20 is illustrated in a raised position relative to the base 8 so as to position the follower 25 at the start of the cam surface 24. Figure 8 illustrates the collar 7 having been rotated clockwise through 90°, and figure 8a illustrates schematically the shuttle 20 having been rotated with the collar 7. This results in the follower 25 (shown in dotted line behind the shoulders 21) sliding along to an apex of the cam surface 24. Figure

9a illustrates the shuttle 20 having been further rotated clockwise through less than 90°, with the actuator 4 approaching the rest position. It should be noted that figure 9a illustrates the cam surface 24 having an end portion 50 that is aligned more vertically than the start 51 of the cam surface 24 as illustrated in figure 7a. The follower 25 is illustrated approaching the end portion 50 and it can be appreciated that the shuttle 20 will move vertically more easily (under the influence of the pump spring 53), allowing the pump head 16 to seal the pump chamber 54, before the collar 7 has completed its rotation to the rest position.

10

In one set of embodiments there is provided a system for transdermal administration of a physiologically active agent from a liquid, the system comprising a device as hereinbefore described wherein the container contains a liquid composition comprising a physiologically active agent.

15

In one set of embodiments the reservoir space of the device is adapted for application to the axilla of a person, particularly the axilla of an adult male.

20

In a further set of embodiments there is provided a method of dispensing a volume of liquid for application to a skin surface including: providing a device as hereinbefore described comprising a container containing the liquid, pumping a volume of liquid from the container through the aperture formed in a the receptacle to the receptacle defining a reservoir space to accommodate the extracted volume of liquid wherein the reservoir space is adapted to substantially collapse when the volume of liquid is applied to the treatment surface.

25

In a preferred set of embodiments the liquid is a liquid pharmaceutical composition for application to at least one axilla of a person and the receptacle is adapted for spreading the liquid over the surface of the axilla of the person.

30

In a further set of embodiments there is provided a method of transdermal administration of a physiologically active agent to a subject including providing a device as hereinbefore described wherein a liquid comprising the

pharmaceutically active agent is contained in the container; pumping a volume of liquid from the container through the aperture formed in a the receptacle to the receptacle defining a reservoir space to accommodate the extracted volume of liquid wherein the reservoir space is adapted to substantially collapse when
5 the volume of liquid is applied to the treatment surface, and spreading the liquid over an area of skin in at least one axilla of the subject.

In another set of embodiments there is provided a method of increasing the testosterone blood level of a person in need thereof comprising applying to at
10 least one axilla of the person a liquid comprising testosterone wherein the liquid is applied by a device hereinbefore described.

The liquid may take the form of a lotion, gel or cream. In one embodiment, the composition is a lotion. In this context, "lotion" is used in its broad descriptive
15 sense to refer to a low- to medium-viscosity topical preparation intended for application to unbroken skin. By contrast, creams and gels have higher viscosity but are considered liquids. The terms lotion, creams and gels include single phase preparations and multiphase preparations, that is, preparations comprising a mixture, such as an emulsion, of immiscible liquids and/or a
20 dispersion containing a solid in finely dispersed form in a liquid medium. The composition is often a true solution, but with increased viscosity so that its viscosity is more similar to that usually associated with a lotion or gel. The viscosity of the composition is preferably from the viscosity of water up to 300 centipoise. The viscosity is more preferably 10 to 40 centipoise. Accordingly
25 the thickener is preferably present in an amount to provide a viscosity of water up to 300 centipoise, preferably 10 to 40 centipoise.

In one set of embodiments the thickener is present in an amount in the range of from 0.01 % to 10 % w/v (preferably from 0.1 % to 5 %w/v of the liquid.
30

The liquid will preferably comprise a volatile liquid, a physiologically active agent and preferably a thickener.

The volatile liquid (also sometimes called a "volatile carrier" or "vehicle") may be any solvent that is pharmacologically suitable and many such solvents are known in the art. One of the advantages of the inclusion of a volatile solvent or volatile carrier is that it facilitates the composition to dry rapidly, allow the absorption of the active agent, and avoid the problems of accidentally dosing others by confining administration to a small area of skin, preferably the axilla. Preferably the volatile liquid is a solvent having a vapour pressure above 35 mm Hg at atmospheric pressure and normal skin temperature of 32 degrees Celsius. Preferably, the solvent is a lower alkyl alcohol or a mixture of such alcohols. Suitable solvents include ethanol, ethyl acetate, isopropanol, acetone, ethyl formate, methyl acetate, methyl ethyl ketone, pentane and chloroform or mixture thereof in the range of about 40 % to 99 % v/v of the composition, preferably from 50 % to 99 % v/v, more preferably from 60 % to 99 % v/v, still more preferably from 70 % to 99 % v/v and most preferably from 80 % to 99 % v/v.

The more preferred volatile solvents are ethanol, isopropanol and mixtures thereof in an amount in the range of about 40 to 99% v/v of the composition, preferably from 50 % to 99 % v/v, more preferably from 60 % to 99 % v/v, still more preferably from 70 % to 99 % v/v and most preferably from 80 % to 99 % v/v.

In one set of embodiments the active agent comprises testosterone.

The amount of active present in the composition will depend on the desired response required and dose to be administered. Generally testosterone will be present at a concentration in the range of from 0.01 % to 15 % w/v of the liquid composition, preferably from 0.01 % to 10 % w/v of the liquid composition, more preferably from 0.1 % to 8 % w/v of the composition and most preferably from 0.1 % to 5 % w/v of the composition such as about 0.5% w/v, about 1% w/v, about 1.5% w/v or 2% w/v of the liquid composition.

Testosterone may be used in the treatment of testosterone deficiency in men and women and the conditions and diseases resulting therefrom. The method is

particularly suited to treatment of testosterone deficiency in adult males. There are number of closely related androgenic compounds which are synthetically derivatized from testosterone and are known to provide the same or a similar physiologic activity. Such compounds include without limitation, testosterone salts, such as acetate, enanthate, cypionate, isobutyrate and propionate salts, undecanoate esters, cyproterone acetate, danazol, finasteride, fluoxymesterone, methyltestosterone, nandrolone decanoate, nandrolone phenpropionate, oxandrolone, oxymetholone, stanozolol, and testolactone.

Testosterone production in both men and women declines naturally with age. Testosterone deficiency may result from disease or damage to the hypothalamus, pituitary gland, or testicles that inhibits hormone secretion and testosterone production, and is also known as hypogonadism. Depending on age, insufficient testosterone production can lead to abnormalities in muscle and bone development, underdeveloped genitalia, and diminished virility.

Testosterone deficiency in men (hypogonadism) may be present at birth (congenital) or may develop later (acquired). It is classified by the location of its cause along the hypothalamic-pituitary-gonadal axis:

- Primary, disruption in the testicles;
- Secondary, disruption in the pituitary; and
- Tertiary, disruption in the hypothalamus.

The most common congenital cause is Klinefelter's syndrome. This condition, which is caused by an extra X chromosome, results in infertility, sparse facial and body hair, abnormal breast enlargement (gynecomastia), and small testes.

Congenital hormonal disorders such as luteinizing hormone-releasing hormone (LHRH) deficiency and gonadotropin-releasing hormone (GnRH) deficiency (e.g., Kallmann's syndrome) also may cause testosterone deficiency.

Other congenital causes include absence of the testes (anorchism; also may be acquired) and failure of the testicles to descend into the scrotum (cryptorchidism).

Acquired causes of testosterone deficiency include chemotherapy; damage occurring during surgery involving the pituitary gland, hypothalamus, or testes; glandular malformation; head trauma that affects the hypothalamus; infection
5 (e.g., meningitis, syphilis, mumps); isolated LH deficiency (e.g., fertile eunuch syndrome); radiation; testicular trauma; and tumors of the pituitary gland, hypothalamus, or testicles.

The invention may be used in the treatment of sexual dysfunction in men and
10 women.

Androgen deficiency in women has been associated with an increased rate of sexual problems or complaints in a number of studies. These problems are frequently encountered in oophorectomized women and those with androgen
15 deficiency from other causes. Hypoactive sexual desire disorder (HSDD) in women is the persistent or recurring deficiency (or absence) of sexual fantasies, thoughts and/or desire for, or receptivity to, sexual activity, which causes personal distress. The cause may be either physiological or psychological or a combination of both. Common physiological etiologies include hormone
20 deficiencies, medications, and surgical interventions. Any disruption of the female hormonal milieu caused by these etiologies can result in decreased sexual desire. The lack of, or a decrease in, sexual desire may also be secondary to poor sexual arousal and response, or to pain associated with sexual activity. Another factor may be difficulty with inability to attain or
25 maintain sufficient sexual excitement, a condition known as female sexual arousal disorder (FSAD).

In one set of embodiments the device containing a liquid comprising testosterone is for use in treatment of an adult male in need thereof. The adult
30 male may be suffering from testosterone deficiency, hypogonadism or other condition in which testosterone therapy is beneficial.

Normal daily production of testosterone in normal young men ranges from 3–10 mg per day with diurnal variation (maximum ~7am declining throughout the

day). The aim of testosterone therapy in men is to deliver physiologic amounts of testosterone to the systemic circulation producing serum testosterone levels within the normal range for healthy men (e.g. 300–1050 ng/dL). The treatment may be used in testosterone deficient men to provide a testosterone levels
5 within the normal range for healthy men (e.g. 300–1050 ng/dL).

In one embodiment, the invention is used to deliver a composition containing testosterone as the active agent to the axilla of a patient, particularly an adult male patient, to result in a blood level of testosterone of at least a
10 predetermined amount. In one embodiment, the predetermined amount is the normal range. In the case of testosterone, the blood level achieved is at least 200 ng/dL, preferably 300-1050 ng/dL in adult males.

The invention may be used in the treatment of a wide variety of conditions responsive to testosterone therapy such as AIDS Wasting Syndrome,
15 micropenis, somatopause, andropause, viropause, or androgen deficiency in adult males (ADAM), anemia from renal dialysis or chronic kidney disease, benign prostatic hyperplasia, acne, diabetes, infertility, periodontal disease, post anabolic steroid abuse, dry eyes, diabetic retinopathy, retinopathy, and Lupus
20 Erythematosis decreased bone density (i.e. osteoporosis), hyperlipemia, predisposition toward prostate cancer, heart disease, angina, and hypertension.

The liquid composition may and preferably will contain a thickening agent. Examples of thickening agents include lipid thickeners such as beeswax, cetyl
25 alcohol and stearyl alcohol; naturally derived thickeners such as celluloses and modified cellulose, gallactomannan gums such as guar gum and xanthan gum and gelatin; synthetic thickeners such as cross-linked acidic polymers (e.g. CARBOMER™ polymers) and polyacrylic acids cross-linked with polyalkenylether (e.g. CARBOPOL™ polymers), polyacrylamides and polyvinyl
30 alcohol; salts such as magnesium aluminium silicates and polyvinylpyrrolidone and cross linked polyvinylpyrrolidone.

Preferred examples of thickening agents include polyvinyl alcohol (PVA); celluloses; modified cellulose and derivatives (such as hydroxypropyl cellulose

(HPC) and hydroxypropylmethyl cellulose (HPMC)); polyvinylpyrrolidone (PVP) (Povidone™); cross-linked polyvinylpyrrolidone; ammonium acryloyldimethyltaurate/VP copolymer (e.g. Aristoflex AVC™); polyethylene glycol (PEG); acrylic acid polymer, polyacrylic acid, carboxyvinyl polymer (e.g. CARBOPOL™) and glycerin and glyceryl polyacrylate (e.g. HISPAGEL™).

The nature of the thickening agent depends not only on the agent itself, but also the proportion in which it is present and the presence or absence of other components. For example, a polymeric thickening agent may increase viscosity by virtue of the presence of cross-linking formed prior to or after inclusion in the composition. Cross-linking may be induced by an activator. For example, hydroxypropylmethylcellulose (HPMC) may optionally be used in a composition with an activator, in which the volatile solvent is a lower alkyl alcohol. The activator may, for example, be used in amounts such as 0.5 % to 3 % w/w or preferably at a concentration of about 2 % w/w. A suitable activator would be sodium chloride.

The thickening agent will often be used to increase the viscosity of the composition containing a solution of the physiologically active agent in the volatile solvent. Given the nature of the volatile solvents, the solution will typically have very low viscosity. The purpose of the thickener is to increase the viscosity of the solution such that the composition is retained in the vicinity of the area of application (such as the axilla) for a brief period of time so as to permit increased uptake of the physiologically active agent at that site. The thickener preferably increases the viscosity to about that of a typical lotion (eg, sunscreen), but not to the point where the composition becomes a gel. The thickener retains its activity in the context of the other components of the composition of the invention. In particular, the thickening agent must remain active and stable in this environment. In one embodiment the composition has a high alcohol content (for example, where the volatile solvent comprises primarily alcohol at greater than 80% v/v), the thickening agent should be effective in a high alcoholic environment. Having these requirements in mind, a skilled person can select several thickening agents from those known in the art. Desirably, a thickening agent also inhibits the solvent evaporation rate from the composition

so as to enhance the so-called "solvent burst" of active agent into the skin at the site of application. In one embodiment the thickening agent includes polyvinylpyrrolidone or PVP (e.g. PovidoneTM).

- 5 It will be appreciated by one skilled in the art that the amount of thickening agent required is a question of degree and compromise with other parameters. It is also known that many thickening agents have peak activity at a particular concentration, and that activity may drop off with higher or lower percentage concentrations. For example, in one embodiment where the composition
10 comprises over 80% alcohol and the thickening agent used is PVP, the desirable concentration of PVP is between 1 and 3%.

The thickening agent may provide a gel by forming a matrix within and around the composition they are in.

15

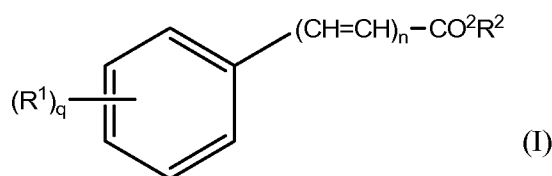
In some embodiments, the thickening agent is an antiperspirant or the composition further includes an antiperspirant and/or a deodorant.

- 20 Despite the inherent antiperspirant and/or deodorant properties of the composition, the composition may be optionally administered with deodorant and antiperspirant additives that do not interfere with the active. In another form, the liquid may comprise at least one physiologically active agent; and at least one volatile solvent; and at least one antiperspirant or deodorant.

- 25 In one embodiment, the composition comprises an antiperspirant agent. The antiperspirant agent may be any suitable substance that reduces or inhibits the production of sweat. In some instances, an antiperspirant agent can also provide deodorancy benefits.

- 30 In one embodiment, the composition may comprise a penetration enhancer. The penetration enhancer is also sometimes called an "absorption" enhancer. Suitable dermal penetration enhancers are described in US Patent 6,299,900 and WO 2006/128255, the contents of each of which are herein incorporated by reference. The preferred dermal penetration enhancers include: fatty acids,

fatty acid esters, fatty alcohols, glycols and glycol esters, 1,3-dioxolanes and 1,3-dioxanes, macrocyclic ketones and lactones containing at least 12 carbon atoms, oxazolidinones and oxazolidinone derivatives, alkyl-2-(N,N-disubstituted amino)-alkanoate esters, (N,N-disubstituted amino)-alkanol alkanoates, 5 sunscreen esters and mixtures thereof. These include the compounds being safe skin-tolerant ester sunscreens of formula:



- 10 wherein R^1 is hydrogen, lower alkyl, lower alkoxy, halide, hydroxy or NR^3R^4 ;
 R^2 is long chain alkyl;
 R^3 and R^4 are each independently hydrogen, lower alkyl or R^3 and R^4 together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocyclic ring;
 15 n is 0 or 1 ; and
 q is 1 or 2.

More preferably the dermal penetration enhancer is selected from the list including oleic acid, oleyl alcohol, cyclopentadecanone (CPE-218TM), 20 pentadecalactone (CPE-215), sorbitan monooleate, glycerol monooleate, propylene glycol monolaurate, polyethylene glycol monolaurate, methyl laurate polyethylene glycol 200, 2-n-nonyl 1,3-dioxolane (SEPATM), dodecyl 2-(N,N-dimethylamino)-propionate (DDAIP) or its salt derivatives, 2-ethylhexyl 2-ethylhexanoate, isopropyl myristate, dimethyl isosorbide, 4-decyloxazolidinon-2- 25 one (SR-38TM, TCPI, Inc.), 3-methyl-4- decyloxazolidinon-2-one, octyl dimethyl-para-aminobenzoate, octyl para-methoxycinnamate, octyl salicylate and mixtures thereof.

Still more preferably the penetration enhancer is octyl para-methoxycinnamate, 30 octyl salicylate or mixture thereof and most preferably the penetration enhancer is octyl salicylate.

The concentration of absorption/penetration enhancer may be in the range from 10-10,000 weight percent of absorption/penetration enhancer based upon the weight of active ingredient. The ratio of penetration enhancer to active
5 ingredient may vary considerably and will be governed as much as anything, by the pharmacological results that are required to be achieved. In principle, it is desirable that as little absorption enhancer as possible is used. However, it is most preferable that octyl salicylate penetration enhancer is present in the range from 0.01 % to 15 % w/v of the total composition. More preferable the
10 octyl salicylate is from 0.1 % to 10 %w/v of the composition and most preferably from 0.5 % to 8 % w/v of the composition.

Preferably the composition is non-occlusive, in that in the broadest sense, the composition is not trapped to the skin, or the skin is not closed to the
15 atmosphere, by means of a patch device, fixed reservoir, application chamber, tape, bandage, sticking plaster, or the like, which remains on the skin at the site of application for a prolonged length of term. Such devices tend to be uncomfortable for the wearer or can be embarrassing or unsightly.

20 In one embodiment, the composition consists essentially of one physiologically active agent, particularly testosterone; one volatile solvent, particularly ethanol, isopropanol or mixture thereof; and one thickener, particularly polyvinylpyrrolidone, each as described above. Preferably, it further includes a penetration enhancer as described above. In one embodiment, the thickener is
25 an antiperspirant, and the composition optionally also includes a deodorant. Each of these embodiments may or may not also include water.

In another embodiment, the composition may include at least one additional active agent and/or at least one additional inactive agent. In a different
30 embodiment, the composition does not include a herbal extract (or like component), whether as a physiologically active agent or otherwise.

The composition may be applied to the skin, including but not limited to axilla, of a subject in any of a range of forms. Suitable forms include for example lotions,

creams and gels. The composition is generally applied in a non-occlusive manner and in the most preferred embodiment the composition is formulated for application as a lotion, gel, cream, foam or viscous solution. Generally, the properties of the composition are such that it can be readily dispensed and spread by the implement of the invention. The composition can be formulated by adding suitable carriers, excipients and thixotropic agents which are inert to the active to facilitate dispensing and spreading of the composition and thus delivery of the composition to the skin for transdermal administration of the active agent.

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The composition may further comprise additional components that will facilitate its preparation into forms suitable for application to the axilla of a subject. Examples of additional components include but are not limited to surfactants, buffers, solvents and propellants.

15

In one set of embodiments the liquid composition comprises:

(a) testosterone in the range of from 0.01 % to 15 % w/v of the liquid composition, more preferably from 0.01 % to 10 % w/v of the liquid composition, more preferably from 0.1 % to 8 % w/v of the composition and most preferably from 0.1 % to 5 % w/v of the composition;

20

(b) ethanol, isopropanol or mixtures thereof in a total amount in the range of from 60% to 99% v/v, preferably from 70 % to 99 % v/v and most preferably from 80 % to 99 % v/v);

25

(c) octyl salicylate in an amount of from 0.01 % to 15 % w/v preferably from 0.01 % to 10 % w/v of the liquid composition, more preferably from 0.1 % to 8 % w/v of the composition, still more preferably from 0.1 % to 5 % w/v of the composition; and optionally

30

(d) a thickening agent.

More specific examples of liquid compositions include the following:

- 0.5 % to 5 % w/v testosterone (more preferably about 2% w/v testosterone);
- 0.1 % to 10 % w/v octyl salicylate;
- 5 70 % to 99 % v/v volatile liquid selected from ethanol, isopropanol and mixtures thereof; and

Optionally a thickening agent, preferably in an amount to provide a viscosity of from greater than that of water to 300 cP

- 10 In one set of embodiments the thickener is selected from the group consisting of polyvinyl alcohol (PVA); celluloses; modified cellulose and derivatives (such as hydroxypropyl cellulose (HPC) and hydroxypropylmethyl cellulose (HPMC)); polyvinylpyrrolidone (PVP); cross-linked polyvinylpyrrolidone; ammonium acryloyldimethyltaurate/VP copolymer; polyethylene glycol (PEG); acrylic acid
- 15 polymer, polyacrylic acid, carboxyvinyl polymer and glycerin and glyceryl polyacrylate in an amount of from 0.1 to 10% w/v (preferably 0.1 to 5%w/v and more preferably 0.5% to 5% w/v) of the liquid composition.

- In the most preferred example the liquid compositions for delivery using the device comprises:
- 20

- 2 % w/v testosterone
- 5 % w/v octisylate;
- 2 % w/v polyvinylpyrrolidone;
- 30 % v/v isopropyl alcohol; and
- 25 to 100 % v/v with 95 % ethanol.

- In one embodiment the device is adapted to dispense a volume of liquid comprising testosterone active agent in an amount of from 5 to 120 mg testosterone (preferably from 10 to 60 mg and most preferably about 30 mg) in
- 30 each actuation of the pump corresponding with full displacement of the pump head.

In one embodiment, the composition comprises a volatile carrier which is a combination of isopropylalcohol and ethanol, a penetration enhancer which is octisalate, an active agent which is testosterone and a thickening agent.

- 5 In another embodiment, the composition may further include a second active agent to provide the composition with additional usage benefits. The second active agent may be selected from any one of the active agents listed above, or herbal extracts and/or cosmetic agents (such as, age spot and keratose removing agents, anti-aging agents, antioxidants, and hydroxy acids).

10

Preferably the second active agent is an antifungal agent. Fungal infections are common in areas of the body having higher production of heat and perspiration.

- 15 In yet another embodiment, the composition may further comprise one or more inactive agents. Such inactive ingredients may be referred to as "additives". Examples of such additives include but are not limited to, humectants, deodorant agents, antiperspirants, pH adjusting agents, preservatives, emulsifiers, occlusive agents (including without limitation patches and film formers), solubilizing agents, colorants, and surfactants (including without
20 limitation anionic surfactants).

The invention is described with reference to the following Example. It is to be understood that the Example is provided by way of illustration of the invention and is not limiting to the scope of the invention.

25

Example 1

- The device for dispensing and applying a volume of liquid to a treatment surface, such as the device of Figures 1 to 9, may be used to apply the following testosterone compositions (i), (ii) or (iii) comprising the components
30 listed, for treatment of testosterone deficiency in adult male subjects.

- (i) 2%w/v testosterone
5%w/v octisalate
2%w/v povidone K-90

- 30%v/v isopropyl alcohol
to 100%v/v with 95% ethanol
- (ii) 2%w/v testosterone
5 5%w/v octisalate
2%w/v povidone K-90
30%v/v isopropyl alcohol
2.5%w/v polyethylene glycol 200
to 100%v/v with with 95% ethanol
- 10 (iii) 2%w/v testosterone
5%w/v octisalate
2%w/v povidone K-90
2.5%w/v polyethylene glycol 200
15 to 100%v/v with isopropyl alcohol

Povidone K-90 is a polyvinylpyrrolidone of average M_w of 360,000.

The device of Figures 1 to 9 may be used with a volume of liquid formulation of composition (i), (ii) or (iii) in the container (3). Composition (i) is the most preferred. Referring to the drawing the collar (7) may be rotated with respect to the base (8) to cause operation of pump (9) to force the liquid testosterone composition out of the container (3) and into reservoir space (10) defined by receptacle (5). The device, held in the hand of the adult male subject, is applied using the receptacle to spread the liquid in the region of one or more of the axilla.

Suitable pumps may dispense volumes in the range of 1ml to 2ml of the compositions (i), (ii) or (iii). Most preferred is a pump which dispenses approximately 1.5ml of liquid (+/- 15%). Typically the pump may be configured to dispense the required doses with between one and four pump actuations (one actuation corresponding with full displacement of the pump head).

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A device for dispensing and applying a volume of liquid to a treatment surface, the device having an axis and including: a container for containing the liquid, a pump for extracting the volume of liquid from the container, an actuator for operating the pump, a receptacle defining a reservoir space for accommodating the extracted volume of liquid which substantially collapses when the volume of liquid is applied to the treatment surface, the receptacle having an aperture formed in a floor thereof through which the volume of liquid enters the reservoir space.
2. A device according to claim 1 wherein the receptacle includes a wall surrounding the floor, at least the wall of the receptacle is resiliently deformable so that in an erect condition it defines at least in part the reservoir space and resiliently deforms when the receptacle collapses.
3. A device according to claim 2 wherein the floor and wall are formed from a thin membrane.
4. A device according to any one of claims 1 to 3 wherein the pump includes a head and a body with the head being movable in the direction of the axis so as to induce the volume of liquid to be expelled out of the head of the pump, the floor of the receptacle being resiliently deformable and operatively associated with the pump head so as to deform when the head is moved.
5. A device according to claim 4 wherein the head is movable towards the body when inducing the volume of liquid to be expelled out of the head of the pump.
6. A device according to claim 5 wherein the reservoir space has a depth, and the floor of the receptacle is movable with the pump head so that the depth of the reservoir space increases when the head is moved towards the body.
7. A device according to any one of the preceding claims including a diffuser which diffuses the liquid as it enters the reservoir space.

8. A device according to claim 7 wherein the diffuser includes a single inlet and multiple outlets to guide the liquid across the floor of the reservoir space.
9. A device according to claim 8 wherein the outlets are oriented relative to the inlet so as to cause the liquid to change direction as it travels from the inlet to the outlets.
10. A device according to any one of the preceding claims wherein the actuator includes a base which is fixed relative to the container, a rotatable member that is rotatable relative to the base, and a shuttle that operatively interacts with the pump, and rotates with the rotatable member, and moves relative to the base in the axial direction when the pump extracts the volume of liquid.
11. A device according to claim 10 including a rack and pawl mechanism associated with the rotatable member and the base to configured to hinder the rotation of the rotatable member in a non-preferred direction.
12. A device according to claim 11 wherein the rack and pawl mechanism is configured to cause a greater level of hindrance to rotation of the rotatable member in the non-preferred direction when the actuator is in a rest position.
13. A device according to claim 12 wherein the rack includes a plurality of teeth of one size and one tooth that has a larger trailing edge, wherein the interaction of the pawl with the larger trailing edge causes said greater level of hindrance.
14. A device according to claim 13 wherein said larger trailing edge is at least 40% greater in depth than a trailing edge of a majority of the teeth.
15. A device according to any one of claims 10 to 14 wherein the actuator includes a cam means so that rotation of the rotatable member causes axial movement of the shuttle from a first position toward a second position.
16. A device according to claim 15 wherein the cam means includes a cam surface on the shuttle and a cam follower on the base, wherein the cam follower moves along the cam surface on rotation of the rotatable member.

17. A device according to claim 16 wherein the cam surface is configured to interact with the follower so as to reduce resistance on the shuttle returning to the first position as the actuator approaches a rest position.

18. A device according to claim 17 wherein the cam surface is shaped with an end portion which is aligned substantially vertically so as to permit the shuttle to return to the first position before the actuator reaches the rest position.

19. A device according to claim any one of claims 10 to 18 wherein the shuttle and rotatable member include guide means to limit movement of the shuttle relative to the rotatable member to movement in the axial direction.

20. A device according to any one of claims 10 to 19 including a stop means for preventing the shuttle from moving in the axial direction unless by way of rotation of the rotatable member.

21. A device according to any one of the preceding claims wherein the pump is a positive displacement pump and the container includes a rigid outer shell and a collapsible inner lining, whereby the liquid is retained in the lining which collapses within the shell upon operation of the pump.

22. A device for dispensing and applying a volume of liquid to a treatment surface, the device including: a container for containing the liquid, a pump for extracting the volume of liquid from the container, an actuator for operating the pump, a receptacle defining a reservoir space for accommodating the extracted volume of liquid, the receptacle is used to apply the liquid to the treatment surface, a cap that covers the receptacle and prevents operation of the actuator when in a closed position and, when in an open position reveals the receptacle and permits operation of the actuator, a latch that interacts with the cap so that in a latch condition retains the cap in the closed position and can be adjusted to a release condition to allow the cap to be moved to the open position.

23. A device according to claim 22 including a base that is fixed relative to the container which includes the latch, whereby the base is configured to resiliently

deform to adjust the condition of the latch between a latch condition and a release condition.

24. A device according to claim 23 wherein the latch includes a pair of tabs on opposed sides of the base, and the base includes a deformation zone adjacent each tab which is resiliently deformable for adjusting the condition of the latch.

25. A device according to claim 24 wherein the cap has a pair of apertures formed adjacent an open end of the cap at opposed sides thereof, whereby each aperture receives one of the tabs when the cap is in the closed position and the latch is in the latch condition.

26. A device according to claim 24 wherein the base includes a seat zone for accommodating the open end of the cap, the seat zone being sized to accommodate the open end of the cap in a friction fit.

27. A device according to claim 26 wherein the seat zone includes an annular wall which engages an inner surface of the cap adjacent the open end, the inner surface overlapping with the annular wall so as to produce the friction fit.

28. A device according to claim 27 wherein the inner surface of the cap overlaps with the annular wall so as to prevent tilting of the cap relative to the base.

29. A device according to claim 28 wherein the inner surface of the cap overlaps with the annular wall so as to require the cap to be moved in an axial direction when moving to the open position.

30. A device according to any one of claims 24 to 29 wherein both deformation zones must be depressed to move the cap to the open position.

31. A device according to any one of claims 22 to 30 wherein the actuator includes a rotatable member that rotates relative to the base to operate the pump, wherein the cap prevents rotation of the rotatable device when the cap is in the closed position.

32. A device according to any one of claims 22 to 31 wherein the receptacle is resiliently deformable so as to collapse when applying the liquid to the treatment surface and deform when the actuator is operated.

33. A device according to any one of the preceding claims wherein the treatment surface is an axilla area of a user's skin.

34. A device according to any one of the preceding claims wherein the container contains the liquid which is in the form of a composition including a physiologically active agent.

35. A device according to claim 34 wherein the physiological active agent is testosterone.

36. A device for dispensing and applying a volume of liquid to a treatment surface, the device having an axis and including: a container for containing the liquid, a pump for extracting the volume of liquid from the container, an actuator for operating the pump, a receptacle defining a reservoir space for accommodating the extracted volume of liquid which substantially collapses when the volume of liquid is applied to the treatment surface, the receptacle having an aperture formed in a floor thereof through which the volume of liquid enters the reservoir space, wherein the reservoir space has a depth, and the floor of the receptacle is movable with operation of the pump head so that the depth of the reservoir space increases while the liquid enters the reservoir space.

37. A system for transdermal administration of testosterone from a liquid the system comprising a device according to any one of the previous claims wherein the container contains a liquid composition comprising testosterone.

38. A system according to claim 37 wherein the reservoir space is adapted for application to the axilla of an adult male.

39. A system according to claim 37 or claim 38 wherein the liquid composition comprises:

- (a) testosterone in a total amount of from 0.1 % to 10 % w/v of the liquid composition;
- (b) ethanol, isopropanol or a mixture thereof in an amount in the range of from 60 % to 99 % v/v of the liquid composition;
- (c) octyl salicylate in an amount of from 0.01 % to 15% w/v of the liquid composition; and optionally
- (d) a thickening agent.

40. A system according to any one of claims 37 to 39 wherein the liquid comprises:

- (a) testosterone in an amount of 0.5 % to 5 % w/v of the liquid composition;
- (b) ethanol, isopropanol or a mixture thereof in a total amount of 80 % to 99 % v/v of the liquid composition;
- (c) octyl salicylate in an amount of from 0.1 % to 8 % w/v of the liquid composition;
- (d) optionally a thickening agent.

41. A system according to any one of claims 37 to 40 wherein the liquid comprises:

- (a) testosterone in an amount of 0.1 % to 5 % w/v of the liquid composition;
- (b) ethanol, isopropanol or a mixture thereof in a total amount of 80 % to 99 % v/v of the liquid composition;
- (c) octyl salicylate penetration enhancer is an amount from 0.1 % to 8 % w/v of the liquid composition; and
- (d) a thickener selected from the group consisting of polyvinyl alcohol (PVA); celluloses; modified cellulose and derivatives (such as hydroxypropyl cellulose (HPC) and hydroxypropylmethyl cellulose (HPMC)); polyvinylpyrrolidone (PVP); cross-linked polyvinylpyrrolidone; ammonium acryloyldimethyltaurate/VP copolymer; polyethylene glycol (PEG); acrylic acid polymer, polyacrylic acid, carboxyvinyl polymer and glycerin and glyceryl

polyacrylate in an amount of from 0.5% to 5% w/v of the liquid composition.

42. A system according to any one of claims 37 to 41 wherein the liquid comprises a thickener in an amount to provide a viscosity in the range of from the viscosity of water up to 300 centipoise.

43. A system according to any one of claims 37 to 42 wherein the thickener is polyvinylpyrrolidone present in an amount in the range of from 1 % to 3 % w/v of the liquid composition.

44. A system according to any one of claims 37 to 43 wherein the liquid is for application to at least one axilla of an adult male person and the receptacle is adapted for spreading the liquid over the surface of the axilla of the adult male person.

45. A system according to any one of claims 37 to 44 wherein the liquid comprises:

2 % w/v testosterone
5 % w/v octisylate;
2 % w/v polyvinylpyrrolidone;
30 % v/v isopropyl alcohol; and
to 100 % v/v with 95 % ethanol.

46. A method of transdermal administration of a physiologically active agent to a subject including providing a device according to any one of claims 1 to 36 wherein a liquid comprising the pharmaceutically active agent is contained in the container; pumping a volume of liquid from the container through the aperture formed in a the receptacle to the receptacle defining a reservoir space to accommodate the extracted volume of liquid, wherein the reservoir space is adapted to substantially collapse when the volume of liquid is applied to the treatment surface; and spreading the liquid over an area of skin in at least one axilla of the subject.

47. A method according to claim 46 wherein the reservoir space is adapted for application to the axilla of an adult male.

48. A method according to claim 46 or claim 47 wherein the liquid composition comprises:

- (a) testosterone in an amount of 0.01 % to 10 % w/v of the liquid composition;
- (b) ethanol, isopropanol or a mixture thereof in a total amount in the range of from 60 % to 99 % v/v of the liquid composition;
- (c) octyl salicylate in an amount of from 0.01 % to 15 % w/v of the liquid composition; and optionally (d) a thickening agent.

49. A method according to any one of claims 46 to 48 wherein the liquid comprises:

- (a) testosterone in an amount of 0.1 % to 5 % w/v of the liquid composition;
- (b) ethanol, isopropanol or a mixture thereof in a total amount of 80 % to 99 % v/v of the liquid composition;
- (c) octyl salicylate in an amount of from 0.1 % to 8 % w/v of the liquid composition;
- (d) optionally a thickening agent.

50. A method according to and one of claims 46 to 49 wherein the liquid comprises:

- (a) testosterone in an amount of 0.1 % to 5 % w/v of the liquid composition;
- (b) ethanol, isopropanol or a mixture thereof in a total amount of 80 % to 99 % v/v of the liquid composition;
- (c) octyl salicylate penetration enhancer in an amount from 0.1 % to 8 % w/v of the liquid composition; and
- (d) a thickener selected from the group consisting of polyvinyl alcohol (PVA); celluloses; modified cellulose and derivatives (such as hydroxypropyl cellulose (HPC) and hydroxypropylmethyl cellulose (HPMC)); polyvinylpyrrolidone (PVP); cross-linked

polyvinylpyrrolidone; ammonium acryloyldimethyltaurate/VP copolymer; polyethylene glycol (PEG); acrylic acid polymer, polyacrylic acid, carboxyvinyl polymer and glycerin and glyceryl polyacrylate in an amount of from 0.5 % to 5 % w/v of the composition.

51. A method according to any one of claims 46 to 50 wherein the liquid comprises a thickener in an amount to provide a viscosity in the range of from the viscosity of water up to 300 centipoise.

52. A method according to any one of claims 46 to 51 wherein the thickener is polyvinylpyrrolidone present in an amount in the range of from 1 % to 3 % w/v of the liquid composition.

53. A method according to any one of claims 46 to 52 wherein the subject is a male suffering testosterone deficiency.

54. A method according to claim 53 wherein the liquid is for application to provide a serum testosterone level in the range of from 300 to 1050 ng/dl.

55. A method of dispensing a volume of liquid for application to a skin surface including: providing a device according to any one of claims 1 to 35 comprising a container containing the liquid, pumping a volume of liquid from the container through the aperture formed in a the receptacle to the receptacle defining a reservoir space to accommodate the extracted volume of liquid wherein the reservoir space is adapted to substantially collapse when the volume of liquid is applied to the treatment surface.

56. A method according to claim 55 wherein the reservoir space is adapted for application to the axilla of an adult male.

57. A method of increasing the testosterone blood level of a person in need thereof comprising applying to at least one axilla of the person a liquid comprising testosterone wherein the liquid is applied by a device according to any one of claims 1 to 30 and the liquid comprises:

- (e) testosterone in an amount of from 0.01 % to 10 % w/v of the liquid composition;
- (f) ethanol, isopropanol or mixture thereof in a total amount of from 10 % v/v to 99 % v/v of the liquid composition;
- (g) octyl salicylate in an amount of from 0.01 % to 15 % w/v of the liquid composition; and
- (h) optionally a thickening agent.

58. A method according to claim 57 wherein the liquid comprises:

- (a) testosterone in an amount of 0.1 % to 5 % w/v of the liquid composition;
- (b) ethanol, isopropanol or a mixture thereof in a total amount of 80 % to 99 % v/v of the liquid composition;
- (c) octyl salicylate in an amount of from 0.1 % to 8 % w/v of the liquid composition;
- (d) optionally a thickening agent.

59. A method according to claim 57 or claim 58 wherein the liquid comprises:

- (a) testosterone in an amount of 0.1 % to 5 % w/v of the liquid composition;
- (b) ethanol, isopropanol or a mixture thereof in a total amount of 80 % to 99 % v/v of the liquid composition;
- (c) octyl salicylate penetration enhancer is an amount from 0.1 % to 8 % w/v of the liquid composition; and
- (d) a thickener selected from the group consisting of polyvinyl alcohol (PVA); celluloses; modified cellulose and derivatives (such as hydroxypropyl cellulose (HPC) and hydroxypropylmethyl cellulose (HPMC)); polyvinylpyrrolidone (PVP); cross-linked polyvinylpyrrolidone; ammonium acryloyldimethyltaurate/VP copolymer; polyethylene glycol (PEG); acrylic acid polymer, polyacrylic acid, carboxyvinyl polymer and glycerin and glyceryl polyacrylate in an amount of from 0.5 % to 5 % w/v of the liquid composition.

60. A method according to any one of claims 57 to 59 wherein the liquid comprises a thickener in an amount to provide a viscosity in the range of from the viscosity of water up to 300 centipoise.

61. A method according to any one of claims 57 to 60 wherein the thickener is polyvinylpyrrolidone present in an amount in the range of from 1 % to 3 % w/v of the liquid composition.

62. A method according to any one of claims 57 to 61 wherein the subject is a male suffering testosterone deficiency.

63. A method according to claim 62 wherein the liquid is for application to provide a serum testosterone level in the range of from 300 to 1050 ng/dl.

64. A method according to any one of claims 57 to 63 wherein the testosterone is present in an amount of about 2 % w/v of the liquid.

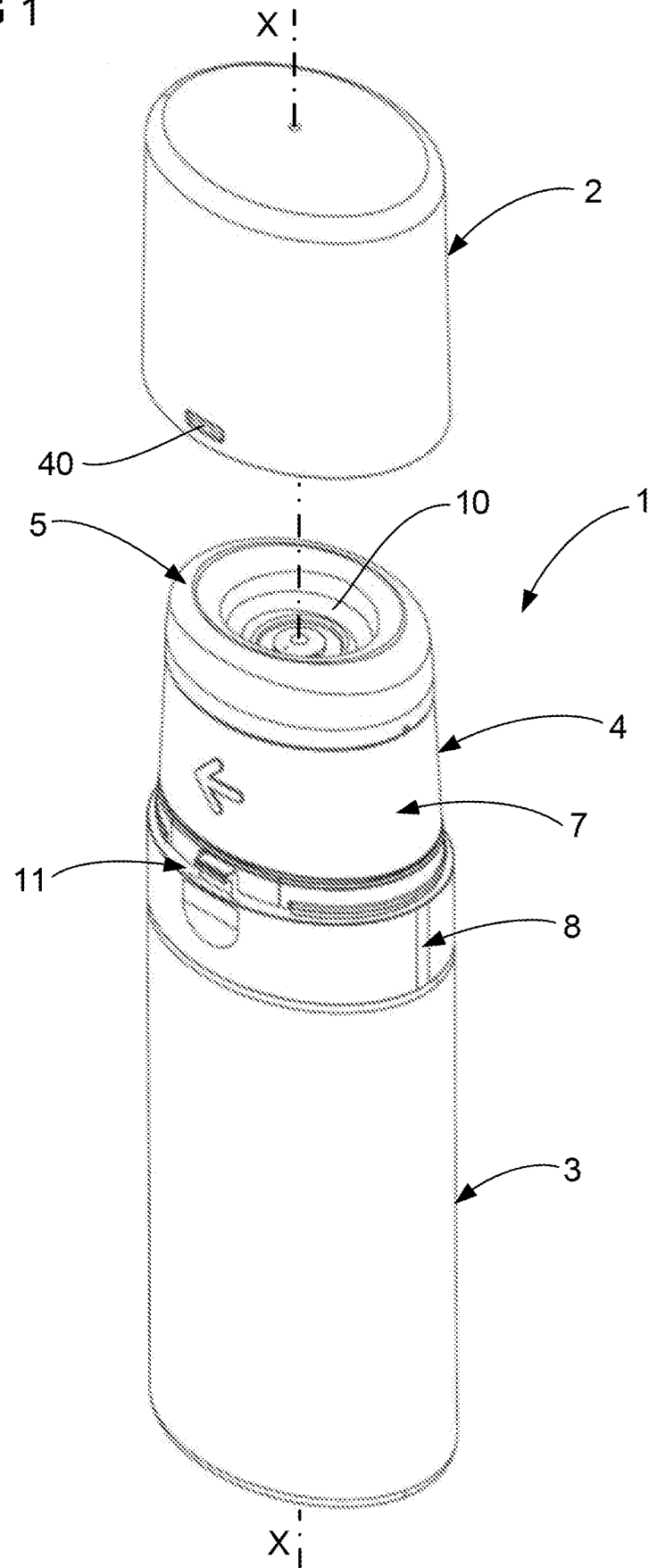
65. A method according to claim 64 wherein the octisalate is present in an amount of 5 % w/v of the liquid composition.

66. A method according to claim 57 wherein the liquid comprises:

- 2 % w/v testosterone
- 5 % w/v octisylate;
- 2 % w/v polyvinylpyrrolidone;
- 30 % v/v isopropyl alcohol; and
- to 100 % v/v with 95 % ethanol.

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FIG 1



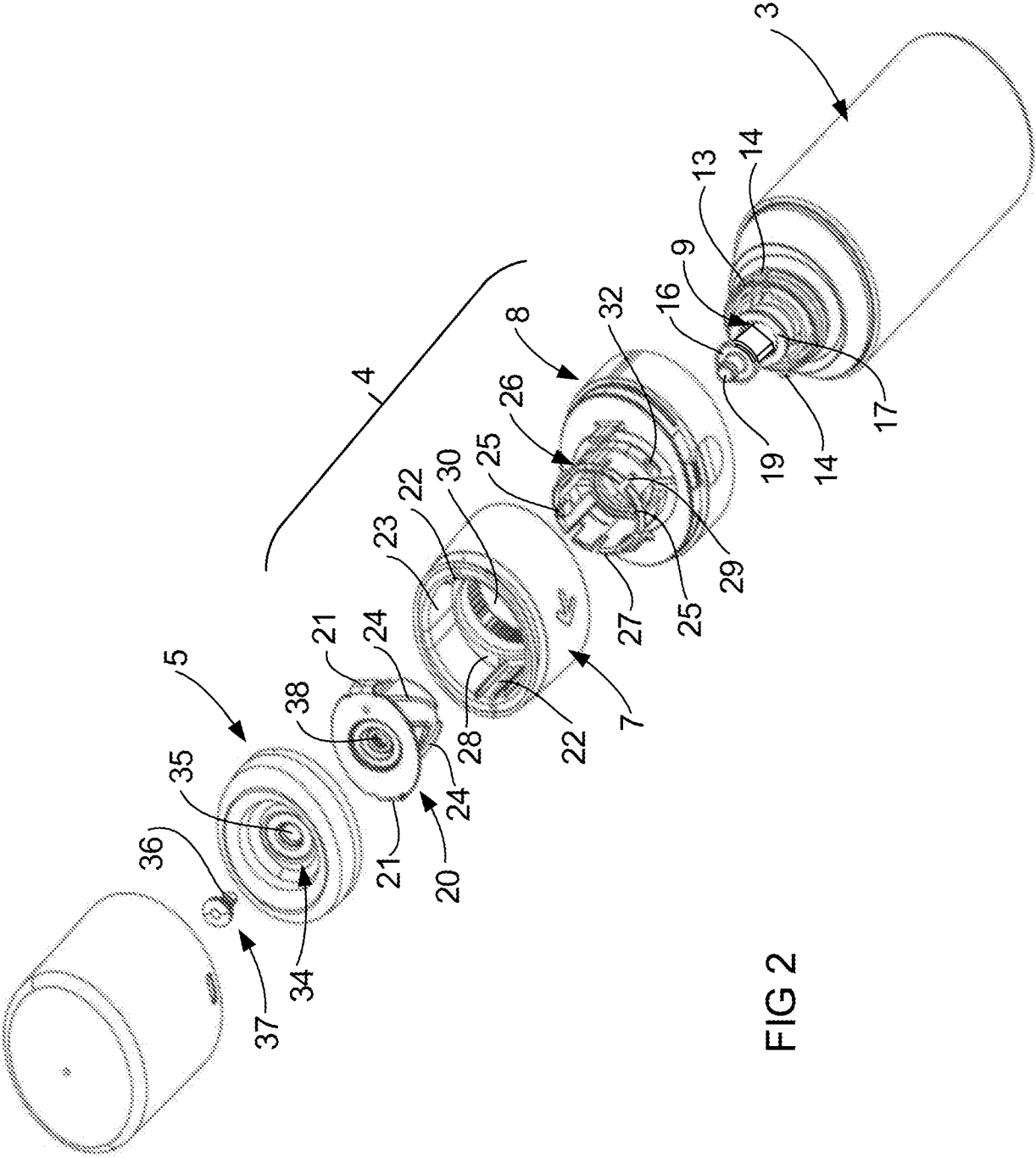
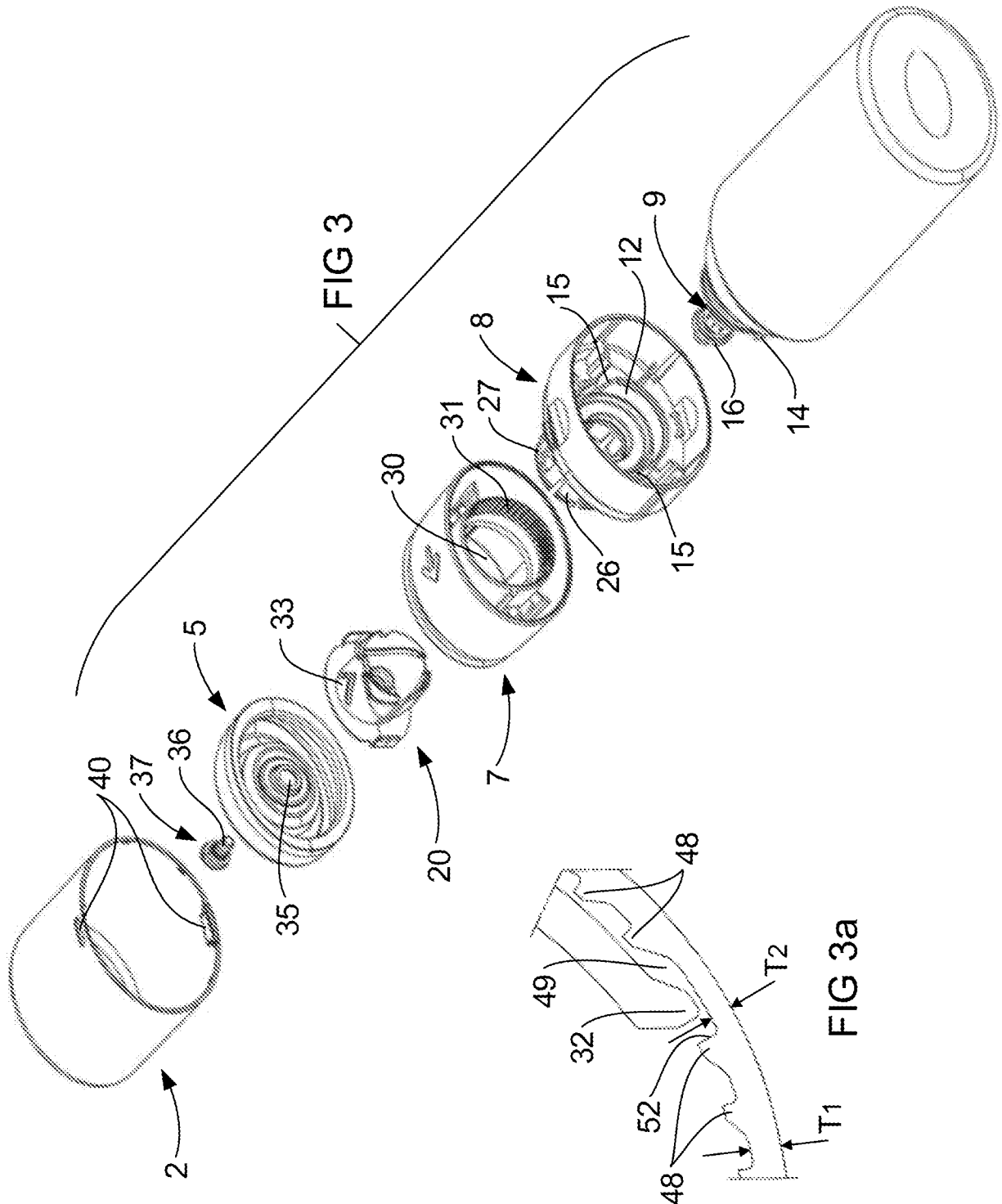


FIG 2



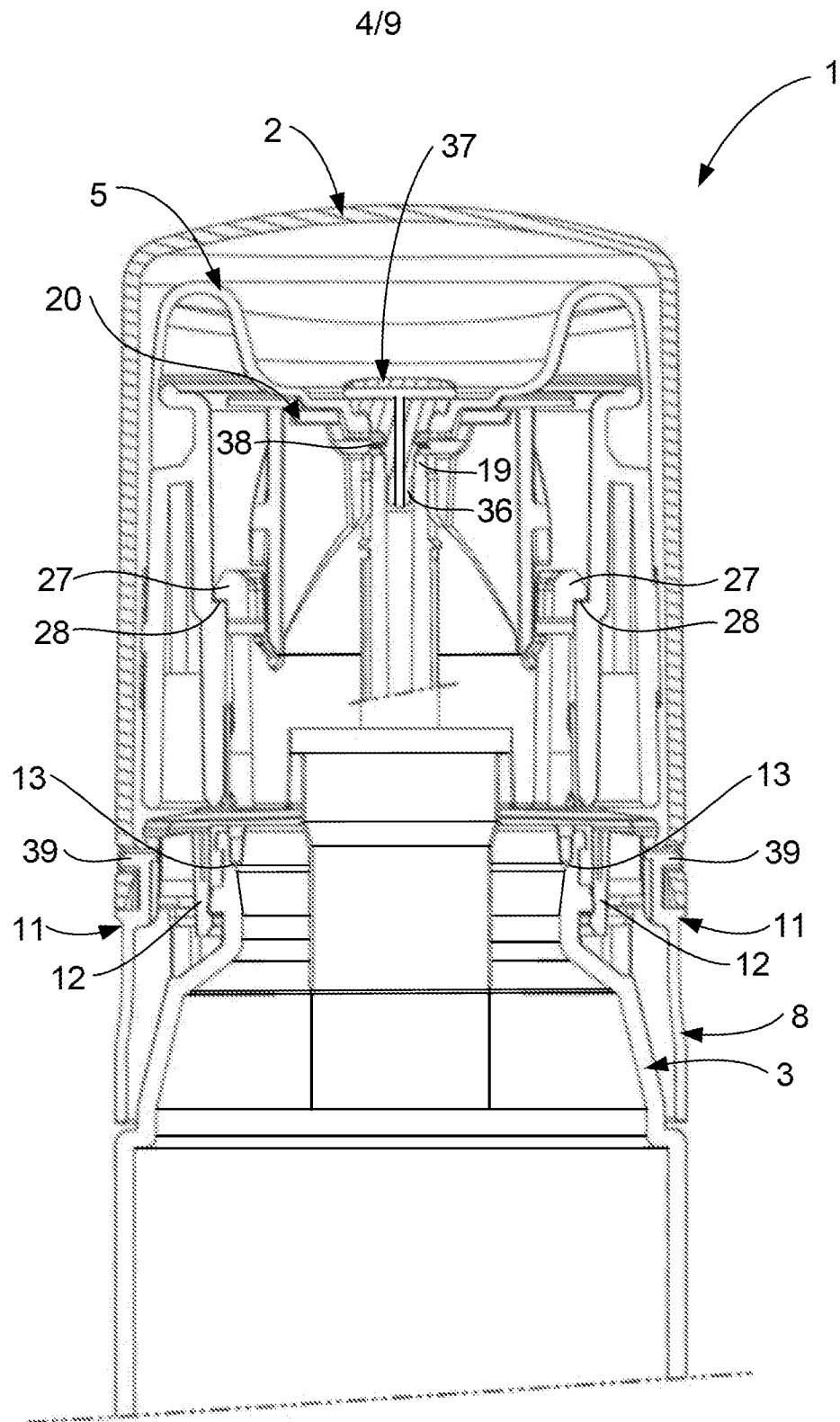


FIG 4

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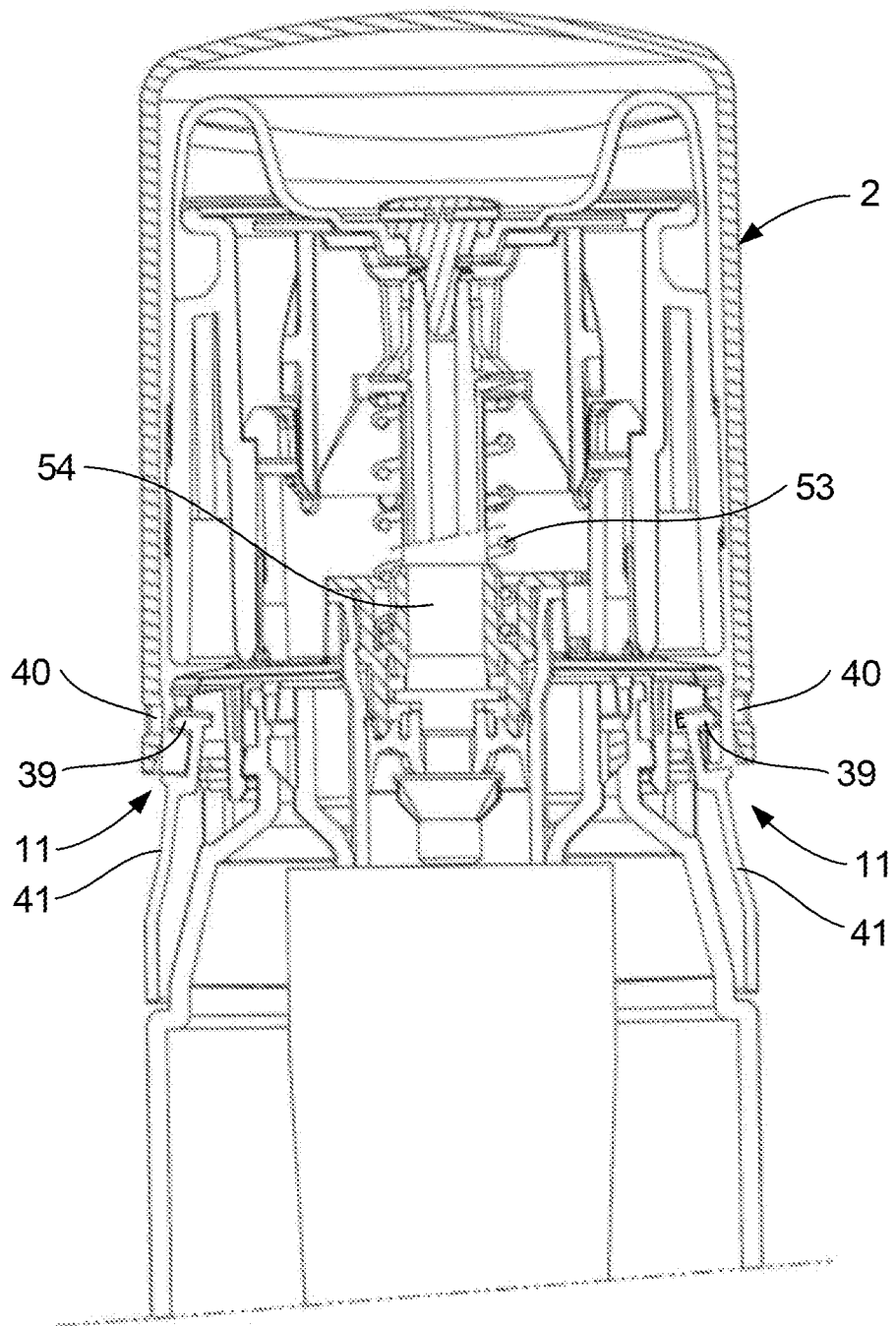


FIG 5

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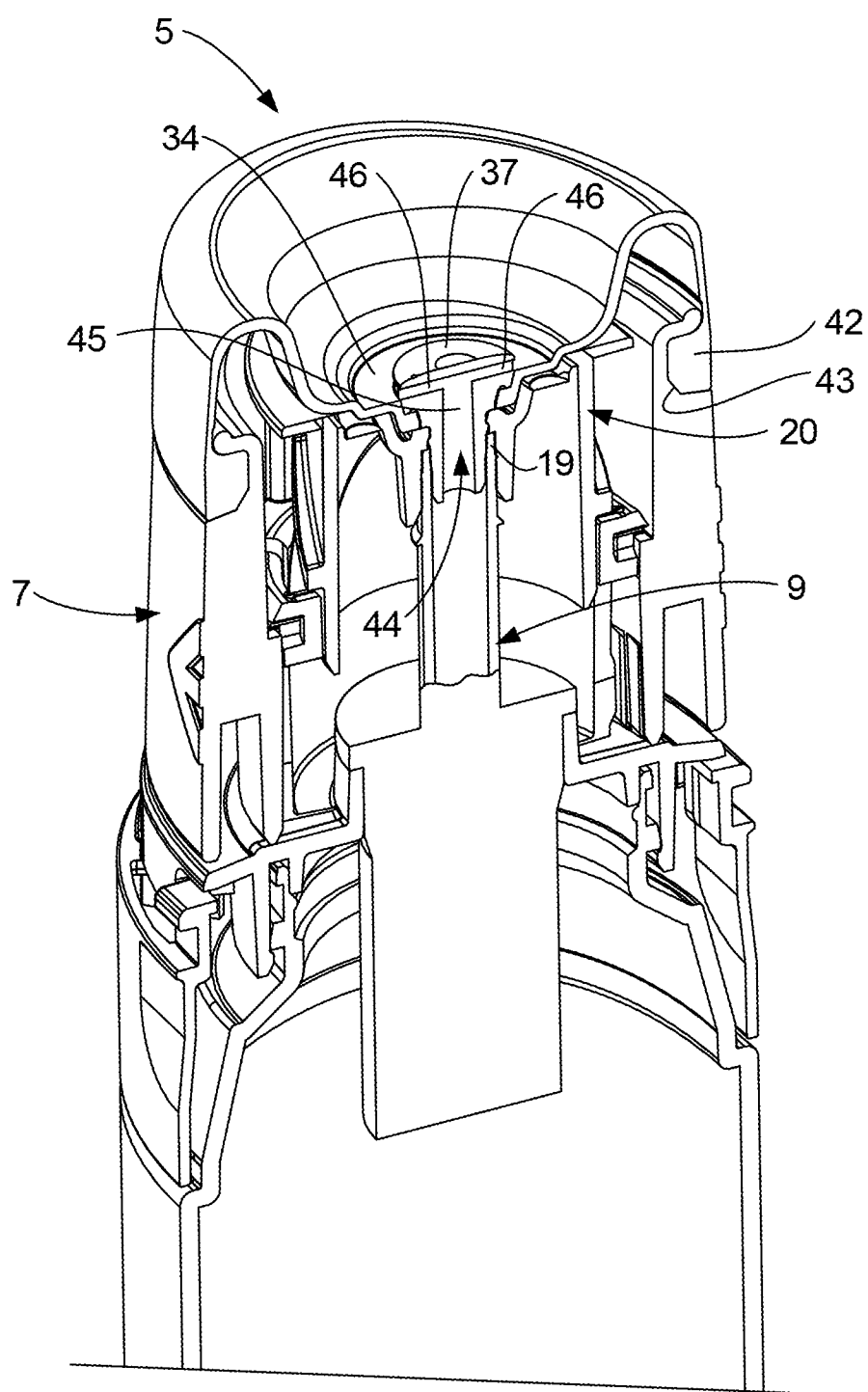


FIG 6

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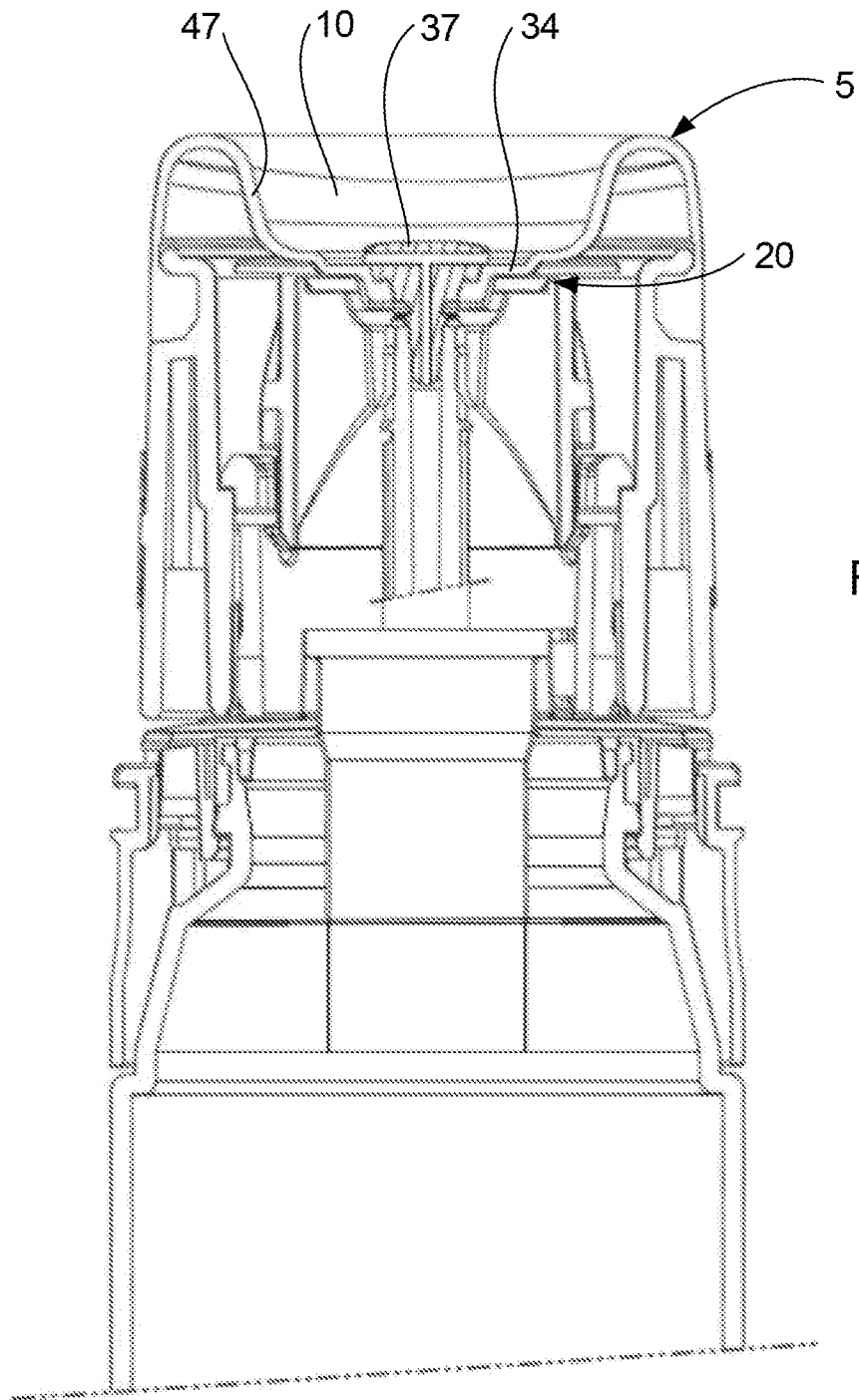


FIG 7

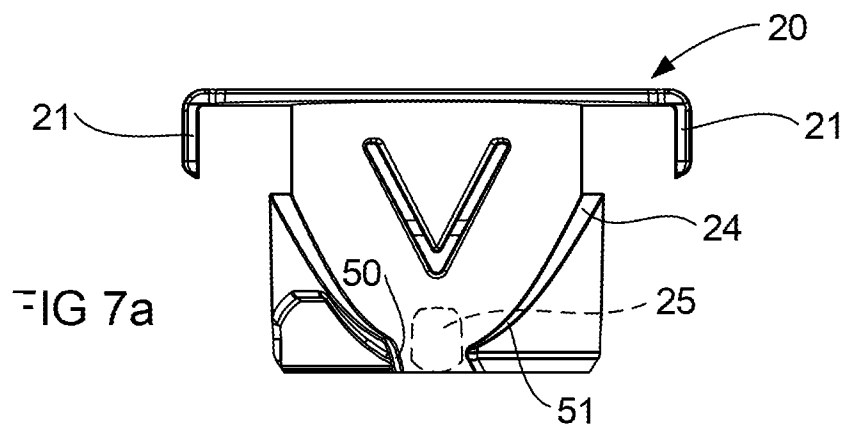


FIG 7a

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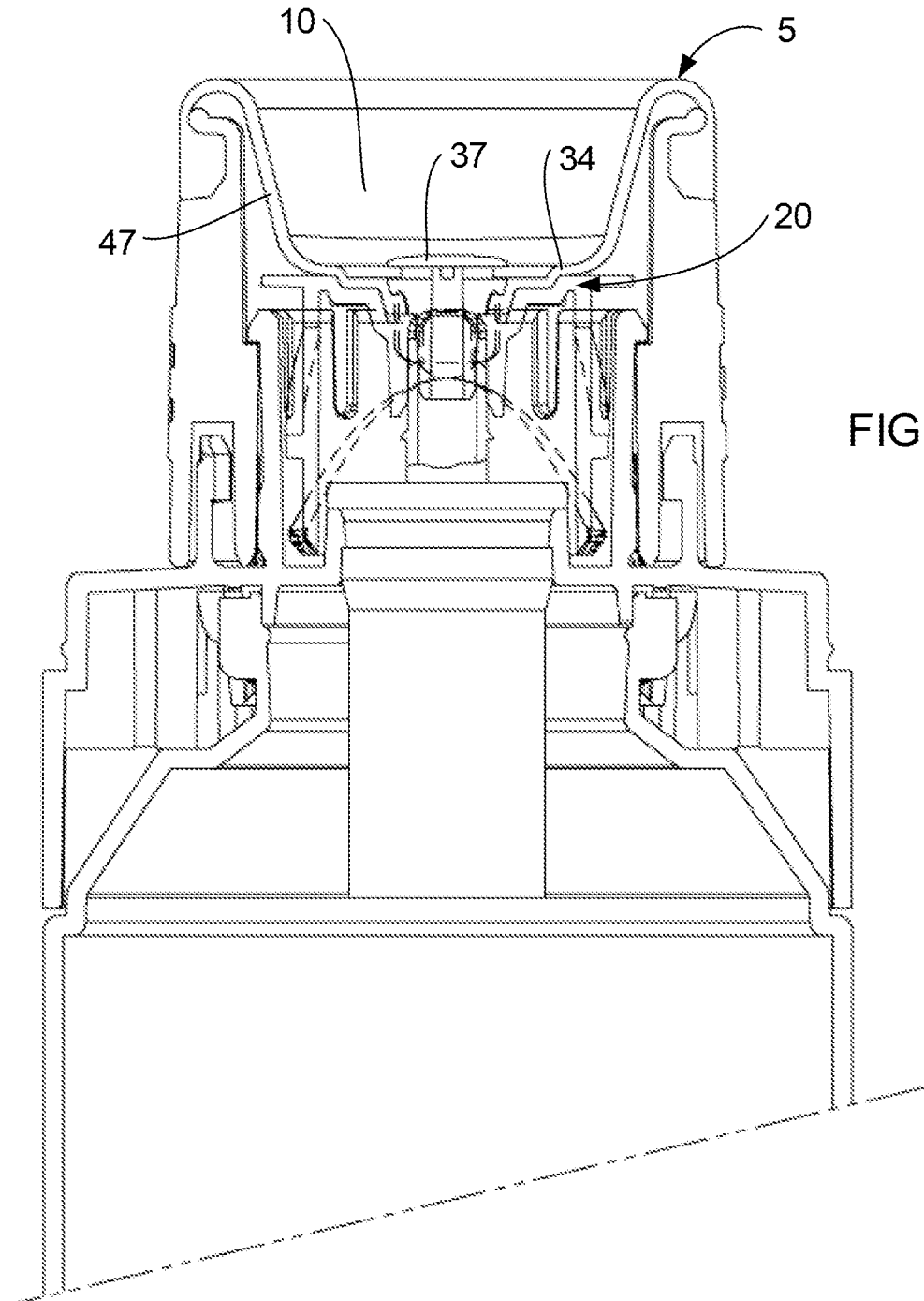


FIG 8

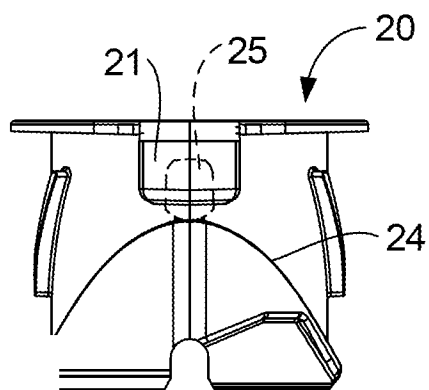


FIG 8a

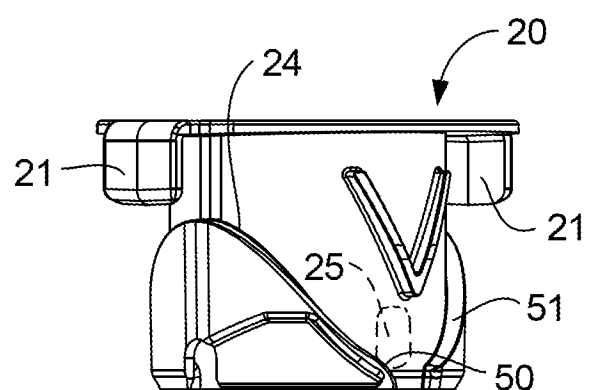


FIG 9a

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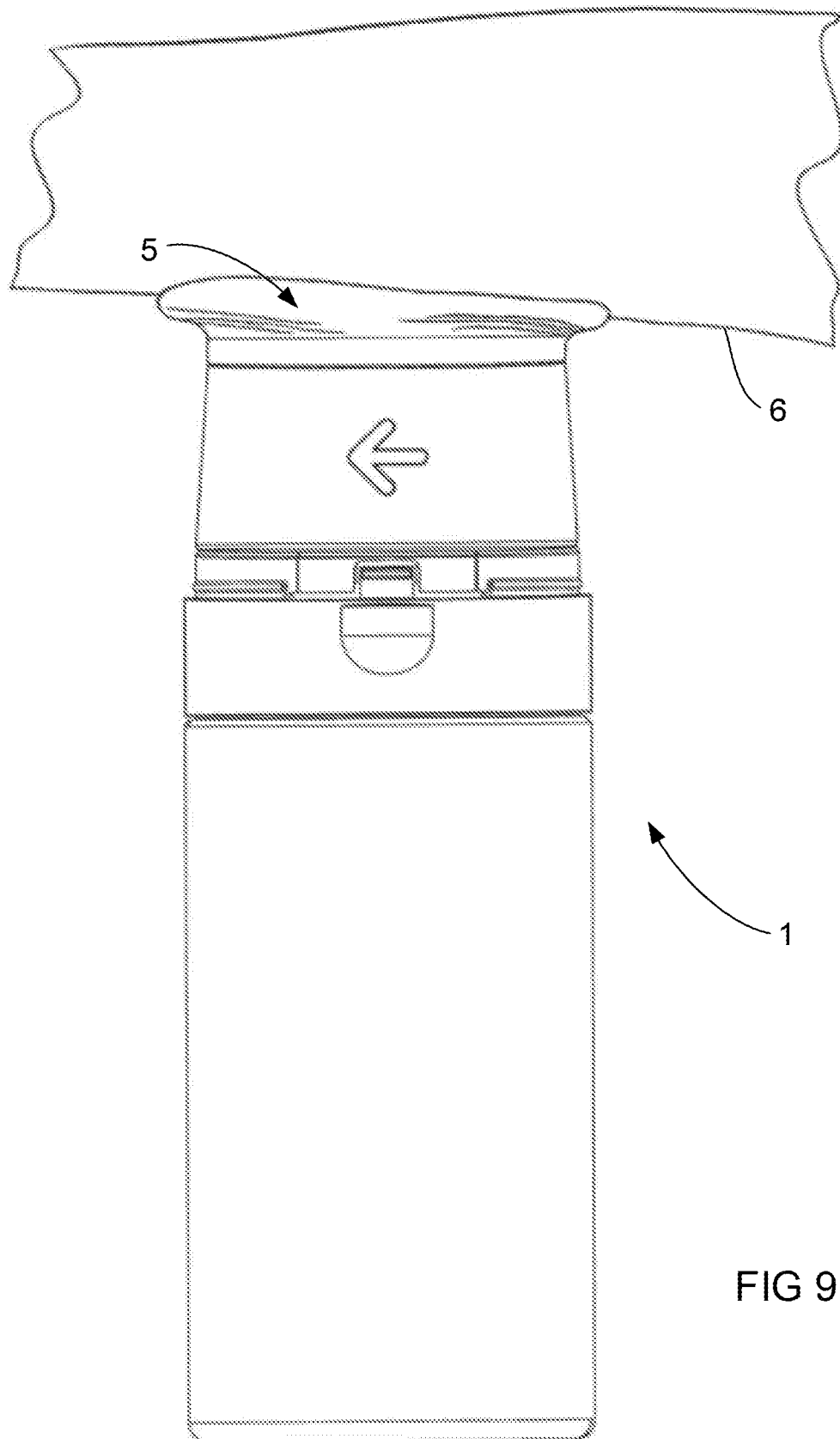


FIG 9

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2014/067351

A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - A61M 35/00 (2015.01) CPC - A61M 35/003 (2015.01) According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC(8) - A45D 34/04; A61M 35/00; B43M 11/06; B65D 47/00, 47/04; G01F 11/28 (2015.01) CPC- A45D 34/04; A61M 35/003; B05B 11/3001; B65D 47/42; B67D 7/163; G01F 11/286 (2015.01) Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched USPC - 222/205, 222/451, 401/205, 401/264 (keyword delimited) Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) Orbit, Patbase, Google Patents, Google Scholar Search terms used: actuator, pump, reservoir, treatment, surface, cap friction, annular, wall, both, depressed, move, liquid, applicator, open, position		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6,758,620 B1 (HARROLD) 06 July 2004 (06.07.2004) entire document	1-6, 36
Y	US 8,118,509 B2 (MARCELLUS) 21 February 2012 (21.02.2012) entire document	1-6, 36
Y	WO 01/01813 A1 (RODIC) 11 January 2001 (11.01.2001) entire document	3
Y	US 2013/0181014 A1 (DECOTTIGNIES et al.) 18 July 2013 (18.07.2013) entire document	4-6, 36
Y	US 7,997,460 B2 (PARDES et al.) 16 August 2011 (16.08.2011) entire document	22-30
Y	US 4,386,714 A (ROBERTO et al.) 07 June 1983 (07.06.1983) entire document	22-30
Y	US 2007/0267100 A1 (SPEAR et al.) 22 November 2007 (22.11.2007) entire document	27-29
☐ Further documents are listed in the continuation of Box C. ☐		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 26 January 2015		Date of mailing of the international search report 12 FEB 2015
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201		Authorized officer: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2014/067351

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.: 7-21, 31-35, 37-66
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:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying 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 report covers 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.:

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.