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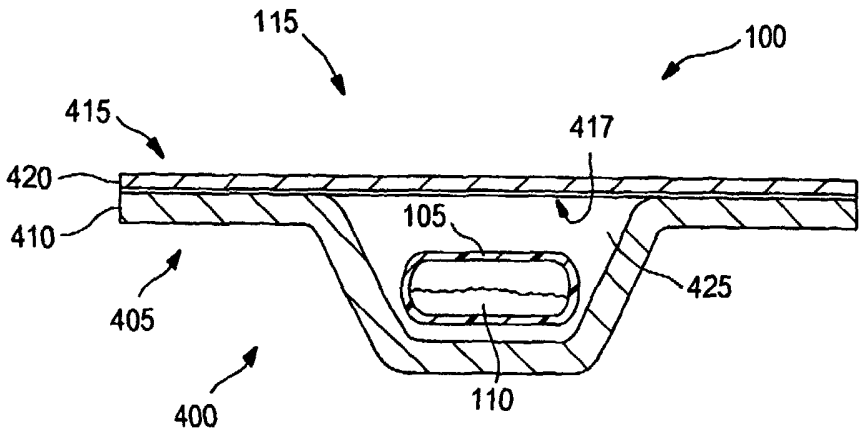

(57) Abstract: A package (100) for storing an aerosolizable pharmaceutical formulation comprises a capsule (105) adapted to contain the aerosolizable pharmaceutical formulation (110), and a moisture barrier (115) around the capsule. The moisture barrier comprises a material that is resistant to moisture passage, whereby the moisture barrier reduces the amount of moisture in contact with the aerosolizable pharmaceutical formulation so that the aerosolizable pharmaceutical formulation may be aerosolized when the capsule is opened. In one version, the moisture barrier comprises a metal.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

CAPSULE PACKAGE WITH MOISTURE BARRIER

BACKGROUND

The need for effective therapeutic treatment of patients has resulted in the development of a variety of pharmaceutical formulation delivery techniques. One traditional technique involves the oral delivery of a pharmaceutical formulation in the form of a pill, capsule, elixir, or the like. However, oral delivery can in some cases be undesirable. For example, many pharmaceutical formulations may be degraded in the digestive tract before they can be effectively absorbed by the body. Inhaleable drug delivery, where an aerosolized pharmaceutical formulation is orally or nasally inhaled by a patient to deliver the formulation to the patient's respiratory tract, has proven to be a particularly effective and/or desirable alternative. For example, in one inhalation technique, a pharmaceutical formulation is delivered deep within a patient's lungs where it may be absorbed into the blood stream. Many types of inhalation devices exist including devices that aerosolize a dry powder, devices comprising a pharmaceutical formulation stored in or with a propellant, devices which use a compressed gas to aerosolize a liquid pharmaceutical formulation, and similar devices.

In one dry powder aerosolization technique, a capsule containing an inhaleable dry powder is loaded into a chamber in an aerosolization device. Within the chamber, the dry powder is at least partially emptied and dispersed to aerosolize the dry powder so that it may be inhaled by a patient. However, in conventional devices, there may be inconsistent aerosolization of the dry powder for some pharmaceutical formulations. As a result, the therapeutic effects of the pharmaceutical formulation may less than ideal.

Therefore, it is desirable to be able to provide a powdered pharmaceutical formulation stored in a capsule that is consistently aerosolizable. It is further desirable to prevent degradation of a pharmaceutical formulation stored in a capsule.

SUMMARY

The present invention satisfies these needs. In one aspect of the invention, a package is provided for storing a capsule which contains an aerosolizable pharmaceutical formulation. The package includes a moisture barrier around the capsule to improve the aerosolization of the pharmaceutical formulation.

In another aspect of the invention, a package for storing an aerosolizable pharmaceutical formulation comprises a capsule adapted to contain the aerosolizable pharmaceutical formulation; and a moisture barrier around the capsule, the moisture barrier comprising a material that is resistant to moisture passage, whereby the moisture barrier reduces the amount of moisture in contact with the aerosolizable pharmaceutical formulation so that the aerosolizable pharmaceutical formulation may be aerosolized when the capsule is opened.

In another aspect of the invention, a package for storing an aerosolizable pharmaceutical formulation comprises a capsule adapted to contain the aerosolizable pharmaceutical formulation, and a bottle adapted to contain a plurality of capsules, the bottle comprising an evacuating mechanism, whereby the bottle reduces the amount of moisture in contact with the aerosolizable pharmaceutical formulation so that the aerosolizable pharmaceutical formulation may be aerosolized when the capsule is opened.

In another aspect of the invention, a package for storing a pharmaceutical formulation comprises a capsule adapted to contain the pharmaceutical formulation, wherein a wall of the capsule comprises a metal, whereby the wall reduces the amount of moisture in contact with the pharmaceutical formulation.

In another aspect of the invention, a package for storing a aerosolizable pharmaceutical formulation comprises a capsule adapted to contain the aerosolizable pharmaceutical formulation, and a multi-layered package around the capsule, the multi-layered package comprising an upper layer and a lower layer, wherein the upper layer and the lower layer each comprise a metal, whereby the multi-layered package reduces the amount of moisture in contact with the aerosolizable pharmaceutical formulation so that the aerosolizable pharmaceutical formulation may be aerosolized when the capsule is opened.

In another aspect of the invention, a method of storing a aerosolizable pharmaceutical formulation comprises containing the aerosolizable pharmaceutical formulation within a capsule, and surrounding the capsule with a moisture barrier to reduce the amount of moisture in contact with the aerosolizable pharmaceutical formulation so that the aerosolizable pharmaceutical formulation may be aerosolized when the capsule is opened.

DRAWINGS

These features, aspects, and advantages of the present invention will become better understood with regard to the following description, appended claims, and accompanying drawings which illustrate exemplary features of the invention. However, it is to be understood that each of the features can be used in the invention in general, not merely in the context of the particular drawings, and the invention includes any combination of these features, where:

Figure 1 is a schematic sectional side view of a package according to the present invention;

Figures 2A through 2C are schematic sectional side views of versions of packages comprising a bottle;

Figures 3A through 3C are schematic sectional side views of versions of packages comprising evacuatable bottles;

Figures 4A and 4B are schematic sectional side views of versions of packages that eject one or more capsules;

Figures 5A and 5B are schematic perspective views of versions of packages comprising a housing with compartments;

Figures 6A through 6C are schematic perspective views of rotary versions of packages comprising a housing with compartments;

Figure 7 is a schematic sectional side view of a version of a package comprising a multi-layered package;

Figure 8 is a schematic sectional side view of another version of a package comprising a multi-layered package;

Figures 9A through 9C illustrate a process of sealing the multi-layered package of Figures 7 or 8;

Figures 10A and 10B are schematic sectional side views of a sealing apparatus at different stages of a sealing process;

Figure 11 is a schematic sectional side view of a version of a package comprising a capsule with a metal containing wall;

Figures 12A through 12C are schematic sectional side views of versions of packages having metal containing layers;

Figure 13 is a schematic sectional side view of a package comprising a capsule shaped multi-layered package; and

Figure 14 is a schematic sectional side view of a sealing apparatus for sealing the package of Figure 13.

DESCRIPTION

The present invention relates to storing a pharmaceutical formulation. Although the process is illustrated in the context of storing a dry powder pharmaceutical formulation in a capsule, the present invention can be used in other processes and should not be limited to the examples provided herein.

A package **100** according to the present invention is shown schematically in Figure 1. The package **100** comprises a first container, such as a capsule **105**, that is capable of being at least partially filled with a pharmaceutical formulation **110**. The capsule **105** contains the pharmaceutical formulation **110** and provides the pharmaceutical formulation **110** with at least some protection against environmental conditions, such as moisture. In addition, the package **100** comprises an additional moisture barrier **115** that is adapted to provide further protection against undesirable amounts of moisture coming in contact with the pharmaceutical formulation **110**.

Some pharmaceutical formulations are particularly sensitive to moisture. For example, some dry powder pharmaceutical formulations that are to be aerosolized and inhaled by a user may become agglomerated when in the presence of excessive moisture. The agglomerations may affect the aerosol

characteristics of the pharmaceutical formulation and reduce the therapeutic effects of the pharmaceutical formulation delivery. Accordingly, the package **100** of the present invention may be adapted to provide sufficient moisture protection over a predetermined amount of time for a particular pharmaceutical formulation. For example, the moisture barrier **115** or the combination of the moisture barrier **115** with the capsule **105** may provide moisture protection for at least about 2 days, more preferably for at least about 1 week, and most preferably for at least about 3 weeks.

The capsule **105** may be of a suitable shape, size, and material to contain the pharmaceutical formulation **110** and to provide the pharmaceutical formulation **110** in a usable condition. For example, the capsule **105** may comprise a wall **120** which comprises a material that does not adversely react with the pharmaceutical formulation. In addition, the wall **120** may comprise a material that allows the capsule **105** to be opened to allow the pharmaceutical formulation **110** to be aerosolized. In one version, the wall **120** comprises one or more of gelatin, hydroxypropyl methylcellulose (HPMC), polyethyleneglycol-compounded HPMC, hydroxyproplycellulose, agar, or the like. Alternatively or additionally, the capsule wall **120** may comprise a polymeric material, such as polyvinyl chloride (PVC). In one version, the capsule **105** may comprise telescopically ajoined sections, as described for example in U.S. Patent 4,247,066 which is incorporated herein by reference in its entirety. The interior of the capsule **105** may be filled with a suitable amount of the pharmaceutical formulation **110**, and the size of the capsule **105** may be selected to adequately contain a desired amount of the pharmaceutical formulation **110**.

The moisture barrier **115** may be sufficiently thick to decrease the amount of moisture that is able to pass through the barrier **115**. In one version, the moisture barrier **115** comprises a material that is resistant to moisture passage in order to reduce the thickness of the barrier **115**. For example, the moisture barrier **115** may comprise one or more metals, such as aluminum or the like, and/or other moisture barrier materials, such as polyamides, polyvinyl chlorides and the like.

In one version, the moisture barrier **115** may comprise a bottle **125** that holds a single dose of an aerosolizable pharmaceutical formulation. For

example, in the version shown in Figure 2A, one or more capsules **105** containing an aerosolizable pharmaceutical formulation are inserted into the body **130** of the bottle **125** and a cap **135** is inserted thereonto. In one version, the bottle **135** is at least partially evacuated or at least a portion of the moisture is otherwise removed as the one or more capsules **105** are inserted. The dose of single dose of the aerosolizable pharmaceutical formulation may be made up of a particular number of capsules selected to deliver a predetermined amount of the pharmaceutical formulation in aerosolized form to a user. For example, as shown in Figure 2A, the single dose may consist of three capsules **105**. Alternatively, the single dose may consist of one, two, or any number of capsules **105**. The cap **135** may be secured to the body **130** by threads, snap-fit, friction fit, or any suitable manner. Preferably the manner of attachment provides sufficient protection against the passage of moisture. To provide even further moisture protection, the moisture barrier **115** may comprise the bottle **125** and an additional layer of protection. For example, in the version shown in Figure 2B, the moisture barrier **115** comprises a metal-containing layer **140** that surrounds the bottle **125**. In one version, the metal containing layer **140** comprises a foil of aluminum that is heat shrunk around the bottle. The foil may be, for example, from about 10 μm to about 100 μm, and more preferably from about 20 μm to about 80 μm. The foil may also be provided with a manner of allowing the foil to be removed, such as tabbing, scoring, or the like. In another version, as shown in Figure 2C, the cap **135** may be removed and the metal-containing layer **140** may serve as the covering to secure the one or more capsules **105** within the body **130** of the bottle **125**.

In another version, the moisture barrier **115** may comprise a bottle **150** that contains multiple doses of an aerosolizable pharmaceutical formulation. Unlike the versions of Figures 2A through 2C, a bottle **150** containing multiple doses of a pharmaceutical formulation may be opened and closed one or more times, and with each opening the capsules **105** within the bottle **150** are subjected to environmental conditions, including potentially undesirable amounts of moisture. Accordingly, in one version, the moisture barrier comprises a bottle **150** that is capable of reducing the effects of the environmental exposure. For example, in the version of Figure 3A, the bottle **150** comprises a body **155** capable of containing

multiple doses of capsules containing an aerosolizable pharmaceutical formulation and a cap **160** that is attachable to the body **155** in a suitable manner to secure the capsules **105** within the body **155**. The bottle **150** also comprises an evacuation mechanism **165**. In the version of Figure 3A, the evacuation mechanism **165** comprises a one-way valve **170** on the body **155** that allows passage of air from within the body **155** to pass out of the body **155** but prevents the passage of air into the body **155**. The evacuation mechanism **165** also comprises a bellows member **175** that has a one-way valve **180** that allows air to pass out of the bellows **175** but not into the bellows **175**. After withdrawing a dose of pharmaceutical formulation, the user secures the cap **160** on the body and then compresses the bellows **175**. Air within the bellows **175** is forced out through the one-way valve **180** on the bellows **175**. The user then expands the bellows **175** or the bellows **175** is designed to automatically expand by the nature of its configuration. As a result of the expansion, air from the body **155** is pulled through the one-way valve **170** thereby at least partially evacuating the body **155** and removing some potentially undesirable moisture. Figure 3B illustrates another version of an evacuation mechanism **165**. In this version, the evacuation mechanism **165** comprises a squeezable bladder **185** that is normally biased into an expanded condition. Squeezing the bladder **185** forces air out the one-way valve **180** and the recovery of the bladder pulls air from the body **155** through the one way valve **170** to at least partially evacuate the body **155**. As shown in the version of Figure 3B, the evacuation mechanism **165** may be provided on the cap **160** to allow for use of a conventional body **155**. Another version of an evacuation mechanism **165** is shown in Figure 3C. In this version, the evacuation mechanism **165** comprises a bi-stable dome **190**. By pressing on the dome **190**, the dome takes on the shape shown by the dotted lines and forces air though the one-way valve **170**. Afterwards, the dome **190** is returned to the position shown by the solid lines by a bias thereby at least partially evacuating the body **155** and at least partially reducing the amount of moisture within the body **155**. In the versions of Figures 3A through 3C, the moisture protection may be further improved by providing a metal-containing layer around, within, or on the interior of the body **155** and/or the cap **160**.

In another version, the moisture barrier **115** may comprise a container **200** that stores capsules **105** containing an aerosolizable pharmaceutical formulation in a reduced moisture environment and ejects a predetermined number of the capsules **105** while maintaining the reduced moisture environment. For example, as shown in Figure 4A, a series of capsules **105** may be stored within an evacuated interior **205** of a cartridge **210**. The cartridge **210** has an end that is covered by a flexible membrane **215** that has a slit **220** near its center. When the flexible membrane **215** is in the position shown in Figure 4A, the slit **220** is closed and air is not allowed to pass through the slit **220**. A capsule **105** is ejected from the cartridge **210** by an ejection mechanism **225**. In the version of Figure 4, the ejection mechanism **225** comprises a plate **230** that is forced into contact with the series of capsules **105** by a compressed spring **235**. A series of notches **240** are provided within the cartridge **210** to prevent or inhibit movement of the plate **230**. When the plate **230** is disengaged from a notch **240** the spring **235** forces the plate **230** toward the flexible membrane **215**. As a result, the plate **230** presses on the series of capsules **105** and the topmost capsule is pressed against the flexible membrane **215** and pressed through the slit **220**. The slit **220** slides around the capsule **105** being ejected and maintains contact with the capsule **105**. In this way, the air is prevented from entering the interior **205** and the interior **205** maintains its reduced moisture condition. After ejection, the plate **230** nestles within the next notch **240**. In the version shown, the plate **230** includes an extension portion **245** that sealingly extends through a slot **250**. The extension portion **245** allows the user to advance the plate **230** from one notch **240** to the next, for example by pulling on the extension. Though the notches **140** are shown as being spaced so as to allow a single capsule **105** to be ejected, they may alternatively be spaced so that multiple capsules **105** may be ejected. Another version of an ejection mechanism **225** is shown in Figure 4B. In this version, interior threads **255** are provided on the interior **205** of the cartridge **210**. The interior threads **255** engage exterior threads **260** on a pushing member **265**. Accordingly, as the pushing member **265** is rotated relative to the cartridge **210**, the pushing member **265** advanced within the interior **205**. Continued rotation will advance the pushing member **265** a sufficient amount to eject the topmost capsule **105** through the slit **215**.

In another version, the moisture barrier **115** comprises a housing **280** having a plurality of compartments **285** that each contain a single dose or a portion of a single dose of an aerosolizable pharmaceutical formulation in a capsule **105**, as shown in Figures 5A and 5B. The compartments **285** may be at least partially evacuated or moisture may be otherwise removed prior to or during insertion of one or more capsules **105** thereinto. The compartments **285** have an opening for accessing the compartment **285**, and a cover member **290** covers the openings. In the version of Figure of Figure 5A, the cover member **290** comprises a slidable plate **295** that may be slid to provide access to a compartment **285**. The slidable plate 295 may ride in grooves or the like (not shown) in the housing **280**. Around each opening on the top of the housing **280** is a seal **299**, such as an o-ring type seal that engages the slidable plate **295** when the slidable plate **295** is positioned over a compartment **285** to prevent excessive moisture from penetrating into the compartment **285**. Another version of a cover member **290** is shown in Figure 5B. In this version, the cover member **290** comprises metal containing layer **300**, such as a foil comprising aluminum, that sealingly covers the compartments **285**. In one version, a spool **305** is provided so that the rotation of the spool **305** causes the metal-containing layer **300** to be removed from a compartment **285**. Figures 6A, 6B, and 6C show rotary versions of a moisture barrier **115** comprises a housing **280** having a plurality of compartments **285** that each contain a single dose or a portion of a single dose of an aerosolizable pharmaceutical formulation in a capsule **105**. In the version of Figure 6A, the cover member **290** comprises a round or circular disc **310** having an opening **315**. The disc **310** includes a bore **320** that may be received on a shaft **325** of the housing **280** so that the disc **310** may rotate relative to the housing **280** to align the opening **315** with a compartment **285**. The seal **299** about the compartment **285** prevents moisture from reaching the compartments **285** before the opening **315** is in alignment. A ratchet or other locking mechanism may be provided to control the relative rotation between the disc **310** and the housing **280**. In the version of Figure 6B, the compartments **285** are provided on the edge of a circular housing **280**, and the cover member **290** comprises a cylinder **330** having an opening **335** that may be aligned with the compartments **285**. A post **340** receives an bore **345** in the housing **280** to provide the rotation between the housing

280 and the cover member **290**, which may be controlled as discussed above. In the version of Figure 6C, the compartments **285** are covered by the metal-containing layer **300**, and a spool **305** is optionally provided to take up the metal-containing layer **300**. The housing **280** and/or the spool **305** may be rotatable by having bores **355, 365** that may be received on respective posts **350, 360**. In one version, a handle may be provided for rotating the spool **305** which in turn causes the body **280** to rotate.

In one version, the moisture barrier comprises a multi-layered package **400**. In one particular version, the multi-layered package **400**, such as a blister, surrounds a capsule **105** containing a pharmaceutical formulation that is susceptible to degradation and/or reduced aerosol performance when exposed to excessive amounts of moisture, such as a dry powder aerosolizable pharmaceutical formulation. The multi-layered package **400** may comprise one or more materials that provide improved moisture barrier properties. For example, the multi-layered package **400** may comprise one or more metals, such as aluminum or the like, and/or other moisture barrier materials. The moisture barrier may be provided below and above the pharmaceutical formulation to provide additional moisture protection. For example, as shown in the version of Figure 7, the multi-layered package **400** may comprise a lower layer **405** comprising a metal containing layer **410** and an upper layer **415** comprising a metal containing layer **420**. The metal containing layers **410, 420** may be sufficiently thick to substantially prevent a significant amount of moisture from passing therethrough. For example, the metal containing layers **410, 420** may be from about 10 μm to about 100 μm, and more preferably from about 20 μm to about 80 μm. The lower layer **405** and the upper layer **415** are sealed together by a layer of sealing material **417**, such as a layer of lacquer that may be from about 1 μm to about 20 μm. Within a cavity **425** is a capsule **105** containing a pharmaceutical formulation, such as a pharmaceutical formulation in dry powder form that may be aerosolized. The lower layer **405** and/or the upper layer **415** of the multi-layered package **400** may optionally include additional materials that serve to improve the sealing or moldability of the layers. For example, Figure 8 shows a particular version of a multi-layered package **400** useful in providing a moisture barrier package for a pharmaceutical formulation. In

this version, the lower layer **405** comprises a first layer **430** comprising polymeric material, such as polyvinyl chloride, and having a thickness of about 60 μm, a second layer **435** comprising a polyamide, such as nylon, and having a thickness of about 25 μm, a third layer **440** comprising a metal, such as aluminum, and having a thickness of about 60 μm, and a fourth layer **445** comprising a polymeric material, such as polyvinyl chloride, and having a thickness of about 60 μm. The upper layer **415** comprises a first layer **450** comprising a metal, such as aluminum, and having a thickness of about 25 μm, and a second layer **455** comprising a sealing material, such as lacquer, and having a thickness of about 6 μm. The multi-layered package **400** comprising a lower layer **405** comprising a metal containing layer **410** and an upper layer **415** comprising a metal containing layer **420** also has the added benefit of protecting the mechanical integrity of the capsule **105**. The metal containing layers provide sufficient rigidity to prevent damage from occurring to the capsule **105** during storage or transport of the capsule **105**. As a result, when the capsule **105** is inserted into an aerosolization device, the chances of consistent aerosolization of the pharmaceutical formulation are increased.

Figures 9A through 9C illustrate a method of sealing the capsule **105** within a multi-layered package **400**. A sealing apparatus **460** comprises a first platform **465** which has a surface **470** which supports a multi-layered package that is to be sealed. The sealing apparatus **460** seals a plurality of layers to one another with the capsule **105** contained between the layers. As shown in Figure 9B, The lower layer **405** of a multi-layered package is placed on the platform surface **470**. The cavity **425** of in the lower layer **405** is positioned within a recess **475** in the surface **470** while a rim portion **480** rests on the surface **470**. The cavity **425** may be formed on the platform **465** and/or the capsule **105** (not shown in Figure 9B) may be inserted into the cavity **425** while the lower layer **405** is positioned on the surface **470**. Alternatively, a lower layer **405** with a preformed cavity **425** prefilled with the capsule **105** may be positioned onto the surface **470**. An upper layer **415** is then, or previously, positioned over the lower layer **130**, as shown in Figure 9C. When the layers are positioned on the first platform **465**, a second platform **485** is lowered toward the first platform **465**. The second platform may be heated so that

it heats the upper layer **415**. The heating and/or compression of the layers **405,415** seals the layers to one another and secures the capsule **105** containing the aerosolizable pharmaceutical formulation within the sealed multi-layered package **400**.

The sealing process is further illustrated in Figures 10A and 10B, which show cross-sectional views before and after the lowering of the second platform **485**, respectively. In Figure 10A, the lower layer **405** is positioned on the platform surface **470** with the cavity **425**, which is filled with a capsule **105** containing the aerosolizable pharmaceutical formulation, positioned within the recess **475**. Alternatively to the configuration shown, the recess **475** may be shaped to more closely resemble the contour of the cavity **425**. The upper layer **415** is positioned over the lower layer **405**. Between the upper layer **415** the lower layer **405** is a sealing material **417** that may cause a seal to be formed between the upper layer **415** and the lower layer **405** when heated and/or compressed. To seal the layers, the second platform **485** is heated and lowered onto the first platform **465** as discussed above and as shown in Figure 10B.

The sealing material **417** is positioned between the upper layer **415** and the lower layer **405** and comprises a material that can seal the upper layer **415** to the lower layer **405** when heat and/or compression is applied to the sandwiched layers. For example, in one version, the sealing material comprises a layer of heat activated sealer, such as lacquer, or polymethyl methacrylate (PMMA), or the like. The heat activated sealer may be provided on the lower surface of the upper layer **415**. When heated to a sufficient temperature, such as at least about 160°C, and often at least about 180°C, the heat activated sealer changes state so that when cooled, the upper layer **415** is sealed to the lower layer **405**. Alternatively, the heat activated sealer may be provided on an upper surface of the lower layer **405** or may be a separate sheet positioned between the upper layer **415** and the lower layer **405**. In another version, the heat activated sealer may be the material of the upper layer **415** and/or the lower layer **405**. In this version, sufficient heat may be applied to melt the material between the layers so that the layers may be fused to one another upon cooling. Alternatively, the sealing material may comprise an adhesive or bonding material that does not require heat to activate.

In another version, the moisture barrier **115** may be provided by the material of the capsule **105**. For example, as shown in Figure 11, the capsule **105** may have a wall **120** that comprises a metal, such as aluminum. In the version shown, an opening **500** is provided in the wall **120** to allow for the dispersion of the pharmaceutical formulation **110** during use. A metal-containing layer **505**, such as a foil comprising aluminum, covers the opening **500**. The metal-containing layer **505** may be heat sealed to the wall **120** and may optionally be provided with a tab by which the cover may be removed by a user prior to use. Alternatively or additionally, the moisture barrier **115** may be provided by a metal-containing layer **505** that is applied around, within, or on the interior of the wall **120** of a capsule **105**. For example, Figure 12A shows of a version of the invention where a metal-containing layer **510** is applied around a capsule that has been filled with an aerosolizable pharmaceutical formulation **110**. The metal-containing layer **510**, such as a foil comprising aluminum, may be heat shrunk onto the capsule **105** or may be otherwise applied. Tabs may be included to allow the foil to be removed from the capsule **105**. Alternatively, the capsule **105** with the foil overwrapping may be inserted into an aerosolization device and the pharmaceutical formulation **110** may be accessed by the capsule opening mechanism utilized by the aerosolization device. In other versions, a metal containing layer **510** may be provided on the interior of the capsule wall **120**, as shown in Figure 12B, or may be within the capsule wall **120**, as shown in Figure 12C.

In another version, as shown in Figure 13, a multi-layered package **400** is formed into a capsule shaped multi-layered package **550**. In this version, the capsule shaped multi-layered package **550** may be filled with an aerosolizable pharmaceutical formulation **110** and may serve and the capsule **105**. For example, the capsule shaped multi-layered package **550** may be placed in an aerosolization device and used by a user. The materials of the upper layer **415** and the lower layer **405** may be as discussed above. For example, the layers may comprise a metal or other moisture barrier material in order to provide sufficient moisture protection for the aerosolizable pharmaceutical formulation within the capsule shaped multi-layered package **550**. A shown in Figure 14, the capsule shaped multi-layered package **550** may be formed in a manner similar to the sealing process described

above in connection with Figures 9 and 10. In this version, the recess **475** in the first platform **465** is sized to accommodate the semi-capsule shaped cavity **555** formed in the lower layer **405**. In addition, a recess **565** is provided in the second platform **485** to accommodate a semi-capsule shaped cavity **560** formed in the upper layer **415**. The platforms **465, 485** compress to heat seal the upper layer **485** to the lower layer **465**, as discussed above, along the rim portions **480**. After sealing, the rim portion **480** may be trimmed to create a smoother profile.

In one version, the package **100** is adapted to contain a dry powder pharmaceutical formulation **110**, as discussed above. The capsule **105** may contain the pharmaceutical formulation in a form where it may be aerosolized for inhalation by the user. For example, when in a powdered form, the powder may be initially stored in the capsule **105**, as described in U.S. Patent 4,995,385, U.S. Patent 3,991,761, U.S. Patent 6,230,707, and PCT Publication WO 97/27892, the capsule being openable before, during, or after insertion of the capsule into an aerosolization device. The powder may be aerosolized by an active element, such as compressed air, as described in US Patent 5,458,135, U.S. Patent 5,785,049, and U.S. Patent 6,257,233, or propellant, as described in US Patent Application 09/556,262, filed on April 24, 2000, and entitled "Aerosolization Apparatus and Methods", and in PCT Publication WO 00/72904. Alternatively the powder may be aerosolized in response to a user's inhalation, as described for example in the aforementioned US Patent Application 09/583,312 and U.S. Patent 4,995,385. All of the above references being incorporated herein by reference in their entireties.

The package **100** of the present invention has been found to be particularly effective when used to store a capsule that is to be used in an aerosolization device that includes a puncturing element, such as the device described in U.S. Patent 4,995,385 and similar devices. The improved moisture protection provided by the package **100** allows for better deagglomeration during the aerosolization process, which results in more finely divided particles for inhalation by the user. In addition, the improved moisture protection prevents the capsule material from becoming brittle. This brittle prevention allows the puncturing element to more efficiently and consistently create one or more openings into the capsule during use. Without the moisture protection, the capsule

may become brittle and may shatter, create capsule particles, and/or have less reproducible openings when punctured. Accordingly, the moisture barrier afforded by the present package **100** provides numerous aerosolization benefits.

In a preferred version, the invention provides a capsule **105** that may be used with a system and method for aerosolizing a pharmaceutical formulation and delivering the pharmaceutical formulation to the lungs of the user. The pharmaceutical formulation may comprise powdered medicaments, liquid solutions or suspensions, and the like, and may include an active agent.

The active agent described herein includes an agent, drug, compound, composition of matter or mixture thereof which provides some pharmacologic, often beneficial, effect. This includes foods, food supplements, nutrients, drugs, vaccines, vitamins, and other beneficial agents. As used herein, the terms further include any physiologically or pharmacologically active substance that produces a localized or systemic effect in a patient. An active agent for incorporation in the pharmaceutical formulation described herein may be an inorganic or an organic compound, including, without limitation, drugs which act on: the peripheral nerves, adrenergic receptors, cholinergic receptors, the skeletal muscles, the cardiovascular system, smooth muscles, the blood circulatory system, synoptic sites, neuroeffector junctional sites, endocrine and hormone systems, the immunological system, the reproductive system, the skeletal system, autacoid systems, the alimentary and excretory systems, the histamine system, and the central nervous system. Suitable active agents may be selected from, for example, hypnotics and sedatives, psychic energizers, tranquilizers, respiratory drugs, anticonvulsants, muscle relaxants, antiparkinson agents (dopamine antagnonists), analgesics, anti-inflammatories, antianxiety drugs (anxiolytics), appetite suppressants, antimigraine agents, muscle contractants, anti-infectives (antibiotics, antivirals, antifungals, vaccines) antiarthritics, antimalarials, antiemetics, anepileptics, bronchodilators, cytokines, growth factors, anti-cancer agents, antithrombotic agents, antihypertensives, cardiovascular drugs, antiarrhythmics, antioxicants, anti-asthma agents, hormonal agents including contraceptives, sympathomimetics, diuretics, lipid regulating agents, antiandrogenic agents, antiparasitics, anticoagulants, neoplastics, antineoplastics, hypoglycemics,

nutritional agents and supplements, growth supplements, antienteritis agents, vaccines, antibodies, diagnostic agents, and contrasting agents. The active agent, when administered by inhalation, may act locally or systemically.

The active agent may fall into one of a number of structural classes, including but not limited to small molecules, peptides, polypeptides, proteins, polysaccharides, steroids, proteins capable of eliciting physiological effects, nucleotides, oligonucleotides, polynucleotides, fats, electrolytes, and the like.

Examples of active agents suitable for use in this invention include but are not limited to one or more of calcitonin, erythropoietin (EPO), Factor VIII, Factor IX, ceredase, cerezyme, cyclosporin, granulocyte colony stimulating factor (GCSF), thrombopoietin (TPO), alpha-1 proteinase inhibitor, elcatonin, granulocyte macrophage colony stimulating factor (GMCSF), growth hormone, human growth hormone (HGH), growth hormone releasing hormone (GHRH), heparin, low molecular weight heparin (LMWH), interferon alpha, interferon beta, interferon gamma, interleukin-1 receptor, interleukin-2, interleukin-1 receptor antagonist, interleukin-3, interleukin-4, interleukin-6, luteinizing hormone releasing hormone (LHRH), factor IX, insulin, pro-insulin, insulin analogues (e.g., mono-acylated insulin as described in U.S. Patent No. 5,922,675, which is incorporated herein by reference in its entirety), amylin, C-peptide, somatostatin, somatostatin analogs including octreotide, vasopressin, follicle stimulating hormone (FSH), insulin-like growth factor (IGF), insulintropin, macrophage colony stimulating factor (M-CSF), nerve growth factor (NGF), tissue growth factors, keratinocyte growth factor (KGF), glial growth factor (GGF), tumor necrosis factor (TNF), endothelial growth factors, parathyroid hormone (PTH), glucagon-like peptide thymosin alpha 1, IIb/IIIa inhibitor, alpha-1 antitrypsin, phosphodiesterase (PDE) compounds, VLA-4 inhibitors, bisphosponates, respiratory syncytial virus antibody, cystic fibrosis transmembrane regulator (CFTR) gene, deoxyreibonuclease (Dnase), bactericidal/permeability increasing protein (BPI), anti-CMV antibody, 13-cis retinoic acid, macrolides such as erythromycin, oleandomycin, troleandomycin, roxithromycin, clarithromycin, davercin, azithromycin, flurithromycin, dirithromycin, josamycin, spiromycin, midecamycin, leucomycin, miocamycin, rokitamycin, andazithromycin, and swinolide A; fluoroquinolones such as

ciprofloxacin, ofloxacin, levofloxacin, trovafloxacin, alatrofloxacin, moxifloxicin, norfloxacin, enoxacin, grepafloxacin, gatifloxacin, lomefloxacin, sparfloxacin, temafloxacin, pefloxacin, amifloxacin, fleroxacin, tosufloxacin, prulifloxacin, irloxacin, pazufloxacin, clinafloxacin, and sitafloxacin, aminoglycosides such as gentamicin, netilmicin, paramecin, tobramycin, amikacin, kanamycin, neomycin, and streptomycin, vancomycin, teicoplanin, rampolanin, mideplanin, colistin, daptomycin, gramicidin, colistimethate, polymixins such as polymixin B, capreomycin, bacitracin, penems; penicillins including penicllinase-sensitive agents like penicillin G, penicillin V, penicillinase-resistant agents like methicillin, oxacillin, cloxacillin, dicloxacillin, floxacillin, nafcillin; gram negative microorganism active agents like ampicillin, amoxicillin, and hetacillin, cillin, and galampicillin; antipseudomonal penicillins like carbenicillin, ticarcillin, azlocillin, mezlocillin, and piperacillin; cephalosporins like cefpodoxime, cefprozil, ceftbuten, ceftizoxime, ceftriaxone, cephalothin, cephapirin, cephalexin, cephradrine, cefoxitin, cefamandole, cefazolin, cephaloridine, cefaclor, cefadroxil, cephaloglycin, cefuroxime, ceforanide, cefotaxime, cefatrizine, cephacetrile, cefepime, cefixime, cefonicid, cefoperazone, cefotetan, cefmetazole, ceftazidime, loracarbef, and moxalactam, monobactams like aztreonam; and carbapenems such as imipenem, meropenem, pentamidine isethiouate, albuterol sulfate, lidocaine, metaproterenol sulfate, beclomethasone diprepionate, triamcinolone acetamide, budesonide acetonide, fluticasone, ipratropium bromide, flunisolide, cromolyn sodium, ergotamine tartrate and where applicable, analogues, agonists, antagonists, inhibitors, and pharmaceutically acceptable salt forms of the above. In reference to peptides and proteins, the invention is intended to encompass synthetic, native, glycosylated, unglycosylated, pegylated forms, and biologically active fragments and analogs thereof.

Active agents for use in the invention further include nucleic acids, as bare nucleic acid molecules, vectors, associated viral particles, plasmid DNA or RNA or other nucleic acid constructions of a type suitable for transfection or transformation of cells, i.e., suitable for gene therapy including antisense. Further, an active agent may comprise live attenuated or killed viruses suitable for use as

vaccines. Other useful drugs include those listed within the Physician's Desk Reference (most recent edition).

The amount of active agent in the pharmaceutical formulation will be that amount necessary to deliver a therapeutically effective amount of the active agent per unit dose to achieve the desired result. In practice, this will vary widely depending upon the particular agent, its activity, the severity of the condition to be treated, the patient population, dosing requirements, and the desired therapeutic effect. The composition will generally contain anywhere from about 1% by weight to about 99% by weight active agent, typically from about 2% to about 95% by weight active agent, and more typically from about 5% to 85% by weight active agent, and will also depend upon the relative amounts of additives contained in the composition. The compositions of the invention are particularly useful for active agents that are delivered in doses of from 0.001 mg/day to 100 mg/day, preferably in doses from 0.01 mg/day to 75 mg/day, and more preferably in doses from 0.10 mg/day to 50 mg/day. It is to be understood that more than one active agent may be incorporated into the formulations described herein and that the use of the term "agent" in no way excludes the use of two or more such agents.

The pharmaceutical formulation may comprise a pharmaceutically acceptable excipient or carrier which may be taken into the lungs with no significant adverse toxicological effects to the subject, and particularly to the lungs of the subject. In addition to the active agent, a pharmaceutical formulation may optionally include one or more pharmaceutical excipients which are suitable for pulmonary administration. These excipients, if present, are generally present in the composition in amounts ranging from about 0.01 % to about 95% percent by weight, preferably from about 0.5 to about 80%, and more preferably from about 1 to about 60% by weight. Preferably, such excipients will, in part, serve to further improve the features of the active agent composition, for example by providing more efficient and reproducible delivery of the active agent, improving the handling characteristics of powders, such as flowability and consistency, and/or facilitating manufacturing and filling of unit dosage forms. In particular, excipient materials can often function to further improve the physical and chemical stability of the active agent, minimize the residual moisture content and hinder moisture uptake,

and to enhance particle size, degree of aggregation, particle surface properties, such as rugosity, ease of inhalation, and the targeting of particles to the lung. One or more excipients may also be provided to serve as bulking agents when it is desired to reduce the concentration of active agent in the formulation.

Pharmaceutical excipients and additives useful in the present pharmaceutical formulation include but are not limited to amino acids, peptides, proteins, non-biological polymers, biological polymers, carbohydrates, such as sugars, derivatized sugars such as alditols, aldonic acids, esterified sugars, and sugar polymers, which may be present singly or in combination. Suitable excipients are those provided in WO 96/32096, which is incorporated herein by reference in its entirety. The excipient may have a glass transition temperature (Tg) above about 35° C, preferably above about 40 °C, more preferably above 45° C, most preferably above about 55 °C.

Exemplary protein excipients include albumins such as human serum albumin (HSA), recombinant human albumin (rHA), gelatin, casein, hemoglobin, and the like. Suitable amino acids (outside of the dileucyl-peptides of the invention), which may also function in a buffering capacity, include alanine, glycine, arginine, betaine, histidine, glutamic acid, aspartic acid, cysteine, lysine, leucine, isoleucine, valine, methionine, phenylalanine, aspartame, tyrosine, tryptophan, and the like. Preferred are amino acids and polypeptides that function as dispersing agents. Amino acids falling into this category include hydrophobic amino acids such as leucine, valine, isoleucine, tryptophan, alanine, methionine, phenylalanine, tyrosine, histidine, and proline. Dispersibility- enhancing peptide excipients include dimers, trimers, tetramers, and pentamers comprising one or more hydrophobic amino acid components such as those described above.

Carbohydrate excipients suitable for use in the invention include, for example, monosaccharides such as fructose, maltose, galactose, glucose, D-mannose, sorbose, and the like; disaccharides, such as lactose, sucrose, trehalose, cellobiose, and the like; polysaccharides, such as raffinose, melezitose, maltodextrins, dextrans, starches, and the like; and alditols, such as mannitol, xylitol, maltitol, lactitol, xylitol sorbitol (glucitol), pyranosyl sorbitol, myoinositol and the like.

The pharmaceutical formulation may also include a buffer or a pH adjusting agent, typically a salt prepared from an organic acid or base. Representative buffers include organic acid salts of citric acid, ascorbic acid, gluconic acid, carbonic acid, tartaric acid, succinic acid, acetic acid, or phthalic acid, Tris, tromethamine hydrochloride, or phosphate buffers.

The pharmaceutical formulation may also include polymeric excipients/additives, e.g., polyvinylpyrrolidones, derivatized celluloses such as hydroxymethylcellulose, hydroxyethylcellulose, and hydroxypropylmethylcellulose, Ficolls (a polymeric sugar), hydroxyethylstarch, dextrates (e.g., cyclodextrins, such as 2-hydroxypropyl-β-cyclodextrin and sulfobutylether-β-cyclodextrin), polyethylene glycols, and pectin.

The pharmaceutical formulation may further include flavoring agents, taste-masking agents, inorganic salts (for example sodium chloride), antimicrobial agents (for example benzalkonium chloride), sweeteners, antioxidants, antistatic agents, surfactants (for example polysorbates such as "TWEEN 20" and "TWEEN 80"), sorbitan esters, lipids (for example phospholipids such as lecithin and other phosphatidylcholines, phosphatidylethanolamines), fatty acids and fatty esters, steroids (for example cholesterol), and chelating agents (for example EDTA, zinc and other such suitable cations). Other pharmaceutical excipients and/or additives suitable for use in the compositions according to the invention are listed in "Remington: The Science & Practice of Pharmacy", 19th ed., Williams & Williams, (1995), and in the "Physician's Desk Reference", 52nd ed., Medical Economics, Montvale, NJ (1998), both of which are incorporated herein by reference in their entireties.

"Mass median diameter" or "MMD" is a measure of mean particle size, since the powders of the invention are generally polydisperse (i.e., consist of a range of particle sizes). MMD values as reported herein are determined by centrifugal sedimentation, although any number of commonly employed techniques can be used for measuring mean particle size. "Mass median aerodynamic diameter" or "MMAD" is a measure of the aerodynamic size of a dispersed particle. The aerodynamic diameter is used to describe an aerosolized powder in terms of its settling behavior, and is the diameter of a unit density sphere having the same

settling velocity, generally in air, as the particle. The aerodynamic diameter encompasses particle shape, density and physical size of a particle. As used herein, MMAD refers to the midpoint or median of the aerodynamic particle size distribution of an aerosolized powder determined by cascade impaction.

In one version, the powdered formulation for use in the present invention includes a dry powder having a particle size selected to permit penetration into the alveoli of the lungs, that is, preferably 10 μm mass median diameter (MMD), preferably less than 7.5 μm, and most preferably less than 5 μm, and usually being in the range of 0.1 μm to 5 μm in diameter. The delivered dose efficiency (DDE) of these powders may be greater than 30%, more preferably greater than 40%, more preferably greater than 50% and most preferably greater than 60% and the aerosol particle size distribution is about 1.0 - 5.0 μm mass median aerodynamic diameter (MMAD), usually 1.5 - 4.5 μm MMAD and preferably 1.5 - 4.0 μm MMAD. These dry powders have a moisture content below about 10% by weight, usually below about 5% by weight, and preferably below about 3% by weight. Such powders are described in WO 95/24183, WO 96/32149, WO 99/16419, and WO 99/16422, all of which are all incorporated herein by reference in their entireties.

Although the present invention has been described in considerable detail with regard to certain preferred versions thereof, other versions are possible, and alterations, permutations and equivalents of the version shown will become apparent to those skilled in the art upon a reading of the specification and study of the drawings. For example, the relative positions of the elements in the expedients for carrying out the relative movements may be changed. Also, the various features of the versions herein can be combined in various ways to provide additional versions of the present invention. Furthermore, certain terminology has been used for the purposes of descriptive clarity, and not to limit the present invention. For example, the use of the terms "upper" and "lower" may be reversed in the specification. Therefore, the appended claims should not be limited to the description of the preferred versions contained herein and should include all such

alterations, permutations, and equivalents as fall within the true spirit and scope of the present invention.

What is claimed is:

1. A package for storing an aerosolizable pharmaceutical formulation, the package comprising:

a capsule adapted to contain the aerosolizable pharmaceutical formulation; and

a moisture barrier around the capsule, the moisture barrier comprising a material that is resistant to moisture passage,

whereby the moisture barrier reduces the amount of moisture in contact with the aerosolizable pharmaceutical formulation so that the aerosolizable pharmaceutical formulation may be aerosolized when the capsule is opened.

2. A package according to claim 1 wherein the capsule comprises HPMC.

3. A package according to claim 1 wherein the moisture barrier comprises aluminum.

4. A package according to claim 1 wherein the moisture barrier comprises a bottle and a metal-containing foil.

5. A package according to claim 1 wherein the moisture barrier comprises an evacuatable bottle.

6. A package according to claim 1 wherein the moisture barrier comprises a cartridge adapted to store and eject a capsule.

7. A package according to claim 1 wherein the moisture barrier comprises a housing having a plurality of sealed compartments.

8. A package according to claim 1 wherein the moisture barrier comprises a multi-layered package.

9. A package according to claim 8 wherein the multi-layered package comprises a metal.

10. A package according to claim 8 wherein the multi-layered package comprises an upper layer and a lower layer and wherein both layers comprise a metal.

11. A package according to claim 8 wherein the multi-layered package comprises an upper layer and a lower layer and wherein both layers comprise aluminum.

12. A package according to claim 1 wherein the moisture barrier comprises a foil wrapped around the capsule.

13. A package for storing an aerosolizable pharmaceutical formulation, the package comprising:

a capsule adapted to contain the aerosolizable pharmaceutical formulation; and

a bottle adapted to contain a plurality of capsules, the bottle comprising an evacuating mechanism,

whereby the bottle reduces the amount of moisture in contact with the aerosolizable pharmaceutical formulation so that the aerosolizable pharmaceutical formulation may be aerosolized when the capsule is opened.

14. A package according to claim 13 wherein the evacuating mechanism comprises an expandable member in communication with a one-way valve on the bottle.

15. A package for storing a pharmaceutical formulation, the

package comprising:

a capsule adapted to contain the pharmaceutical formulation, wherein a wall of the capsule comprises a metal,

whereby the wall reduces the amount of moisture in contact with the pharmaceutical formulation.

16. A package according to claim 15 wherein the wall comprises aluminum.

17. A package for storing a aerosolizable pharmaceutical formulation, the package comprising:

a capsule adapted to contain the aerosolizable pharmaceutical formulation; and

a multi-layered package around the capsule, the multi-layered package comprising an upper layer and a lower layer, wherein the upper layer and the lower layer each comprise a metal,

whereby the multi-layered package reduces the amount of moisture in contact with the aerosolizable pharmaceutical formulation so that the aerosolizable pharmaceutical formulation may be aerosolized when the capsule is opened.

18. A package according to claim 17 wherein the upper layer and the lower layer each comprise aluminum.

19. A package according to claim 17 wherein the upper layer and the lower layer each comprise a metal-containing foil.

20. A package according to claim 19 wherein the metal-containing foil of each of the layers has a thickness of from about 10 μm to about 100 μm.

21. A method of storing a aerosolizable pharmaceutical formulation, the method comprising:

containing the aerosolizable pharmaceutical formulation within a capsule; and

surrounding the capsule with a moisture barrier to reduce the amount of moisture in contact with the aerosolizable pharmaceutical formulation so that the aerosolizable pharmaceutical formulation may be aerosolized when the capsule is opened.

22. A method according to claim 21 wherein the step of surrounding comprises sealing an upper layer of a multi-layered package to a lower layer of a multi-layered package.

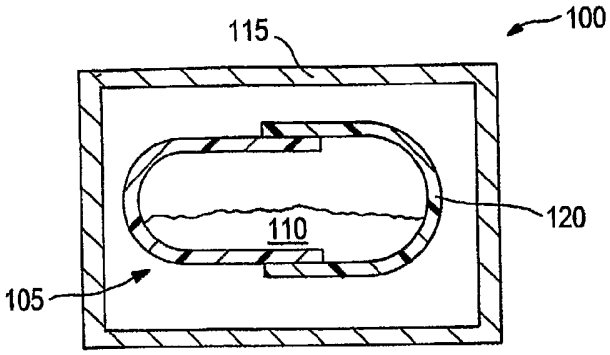


FIG. 1

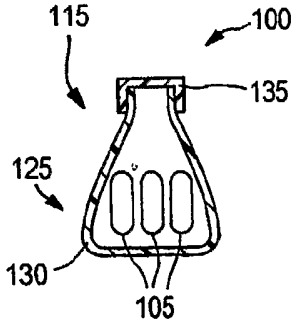


FIG. 2A

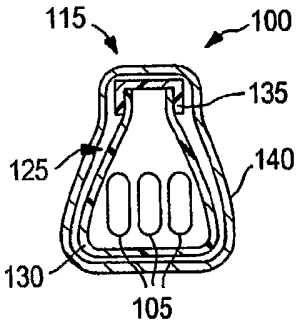


FIG. 2B

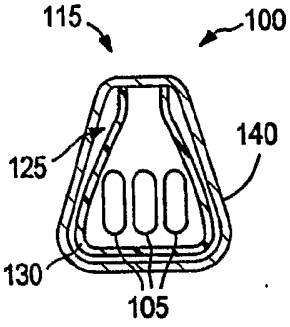


FIG. 2C

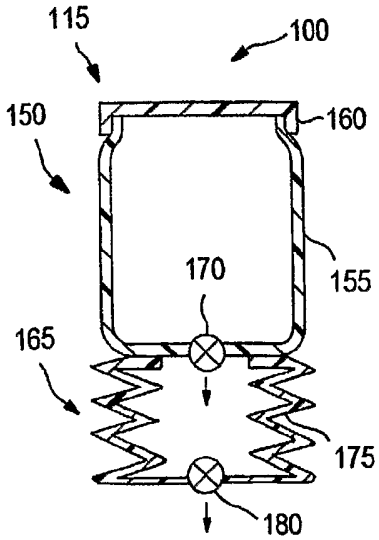


FIG. 3A

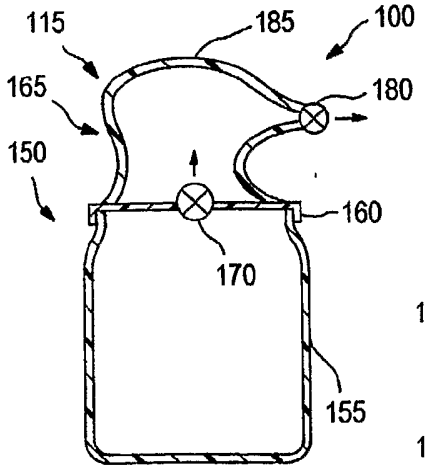


FIG. 3B

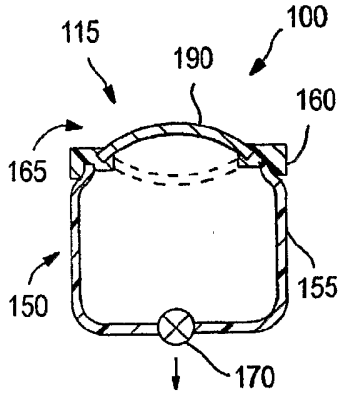


FIG. 3C

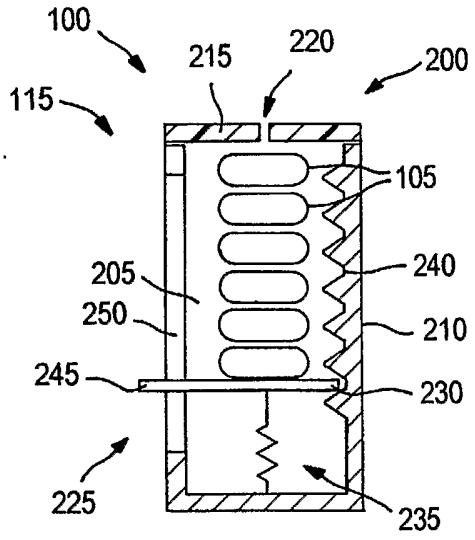


FIG. 4A

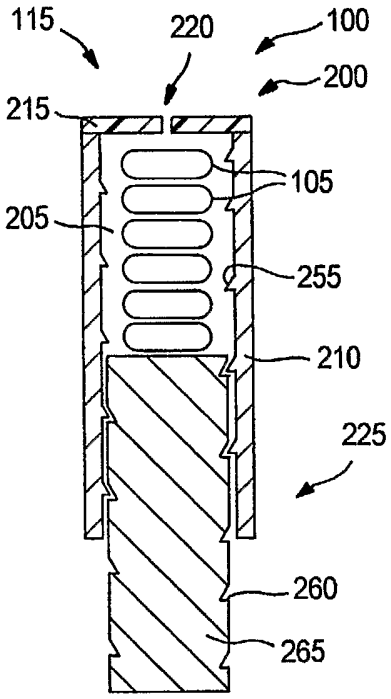


FIG. 4B

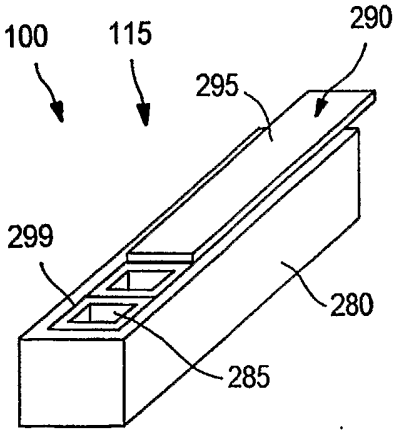


FIG. 5A

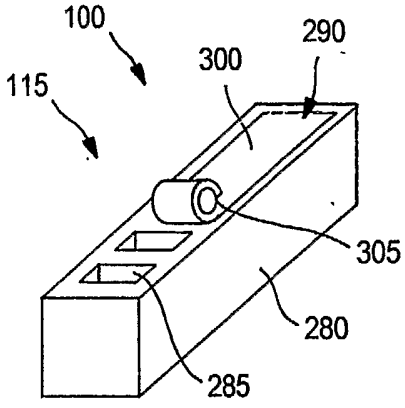


FIG. 5B

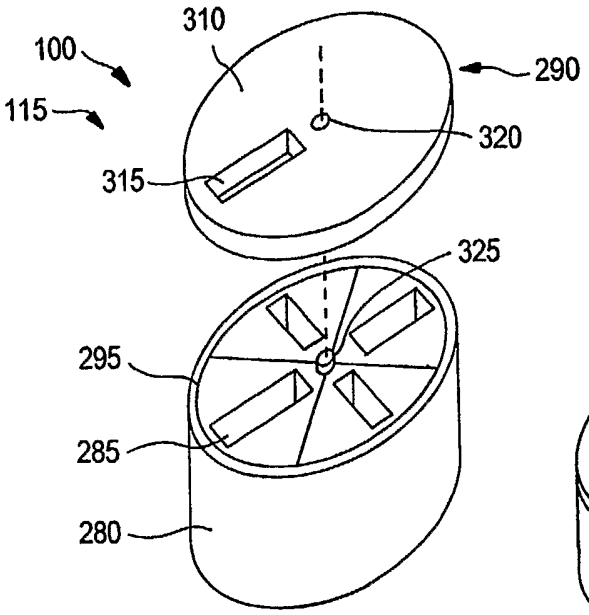


FIG. 6A

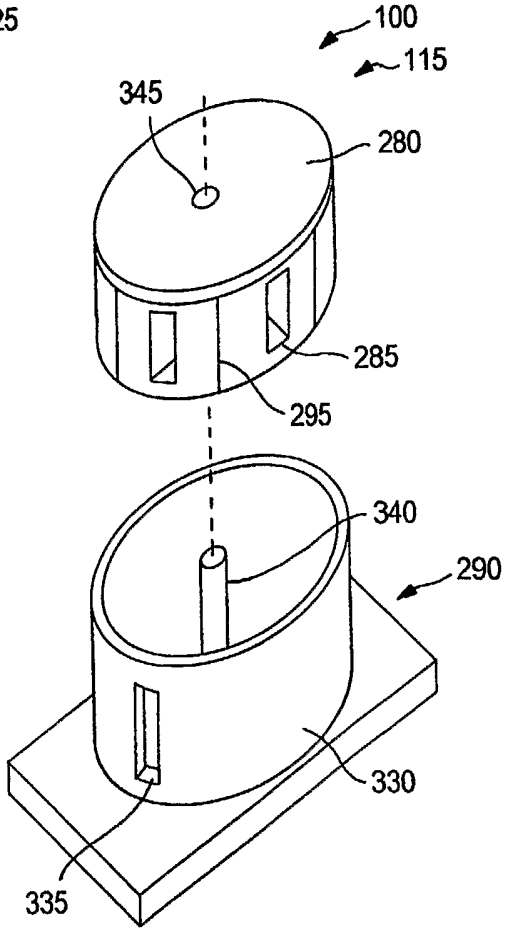


FIG. 6B

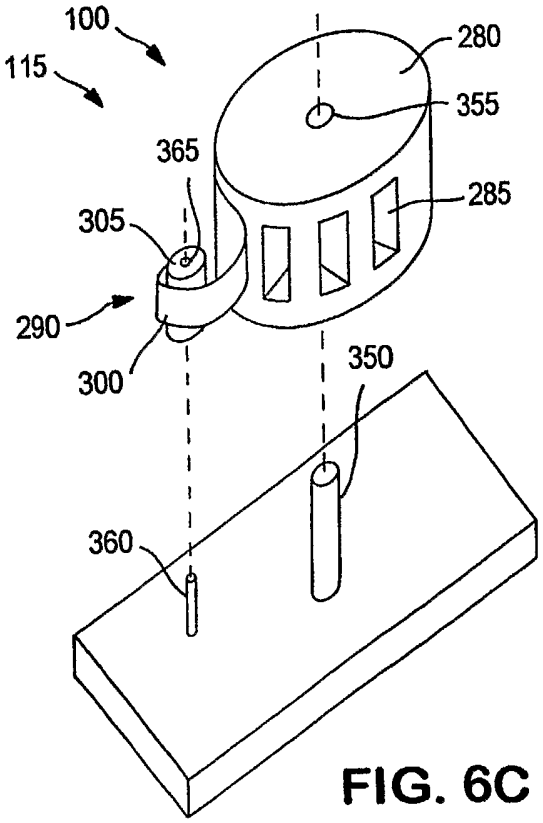


FIG. 6C

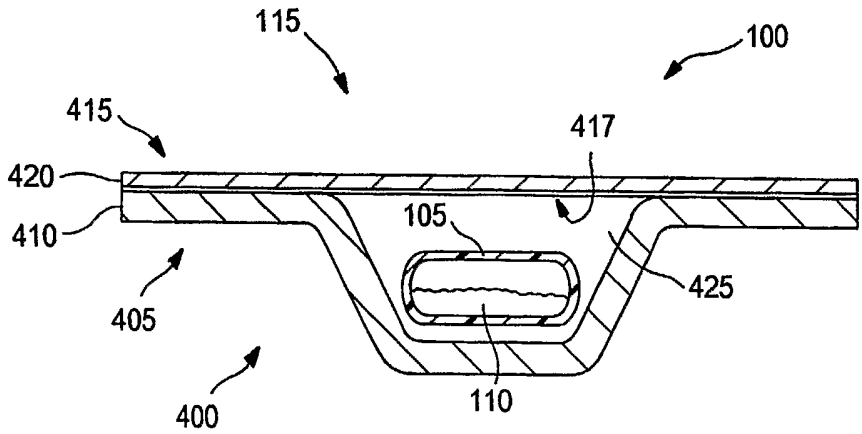

115
100
415
417
420
410
105
425
405
400
110

FIG. 7

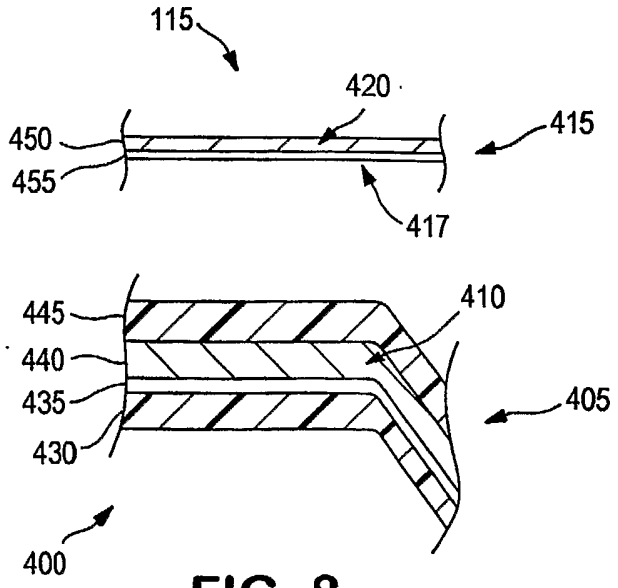

115
420
450
415
455
417
445
410
440
435
405
430
400

FIG. 8

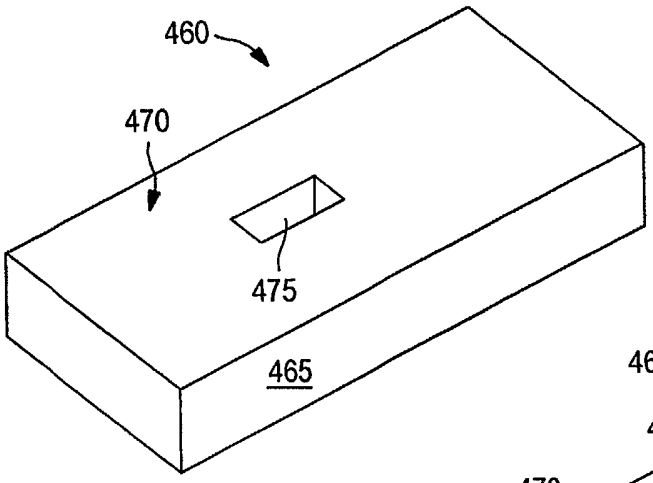


FIG. 9A

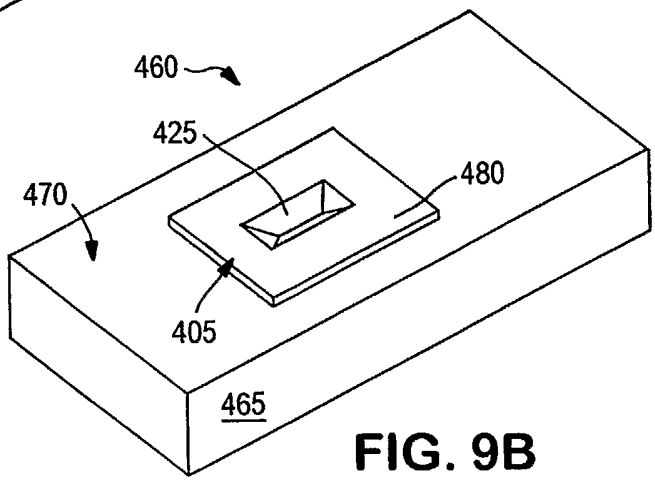


FIG. 9B

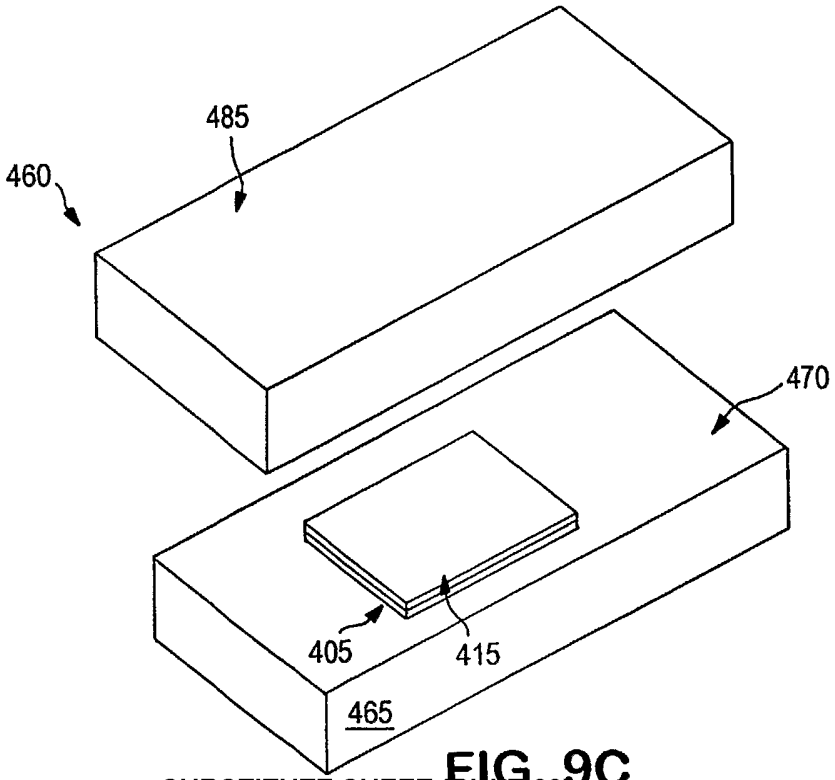


FIG. 9C

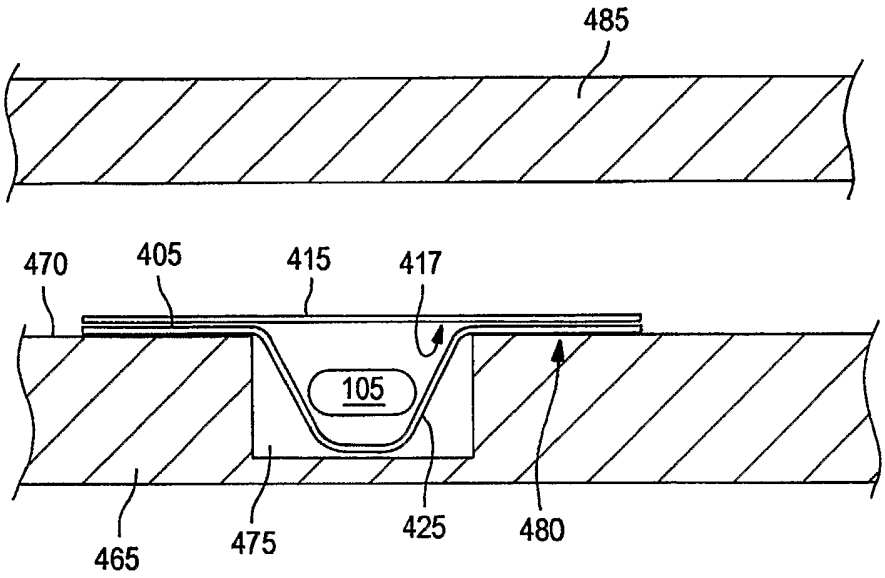


FIG. 10A

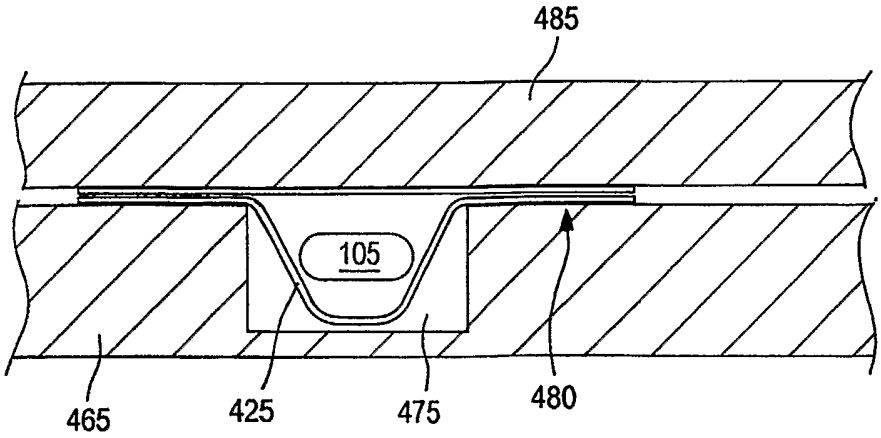


FIG. 10B

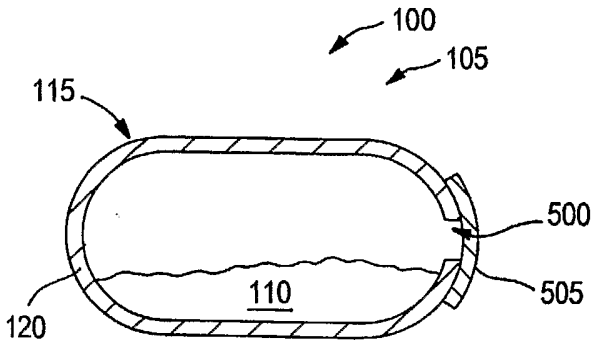


FIG. 11

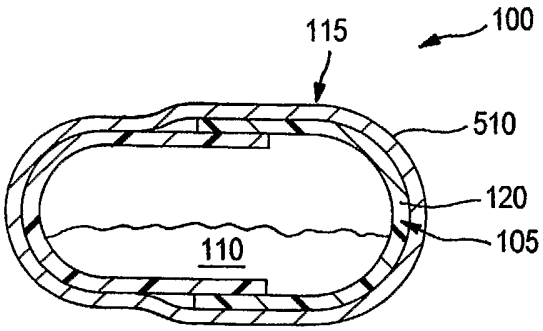


FIG. 12A

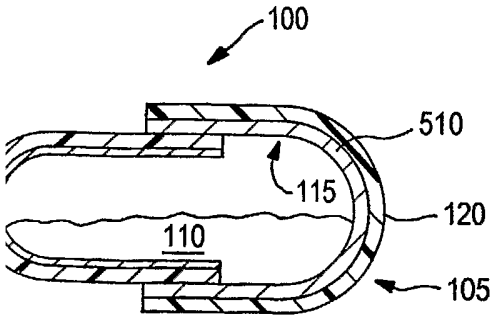


FIG. 12B

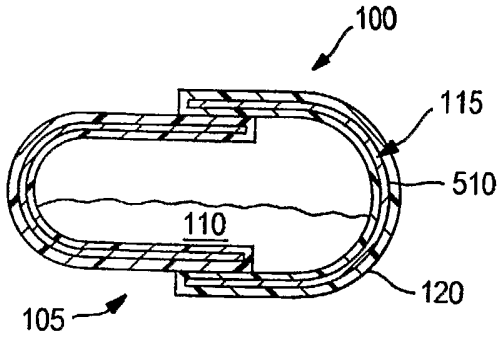


FIG. 12C

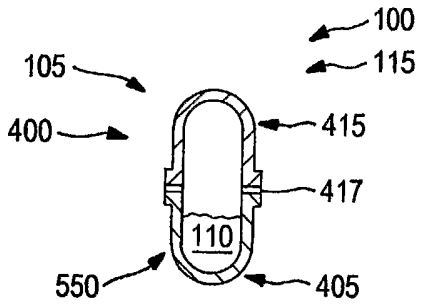
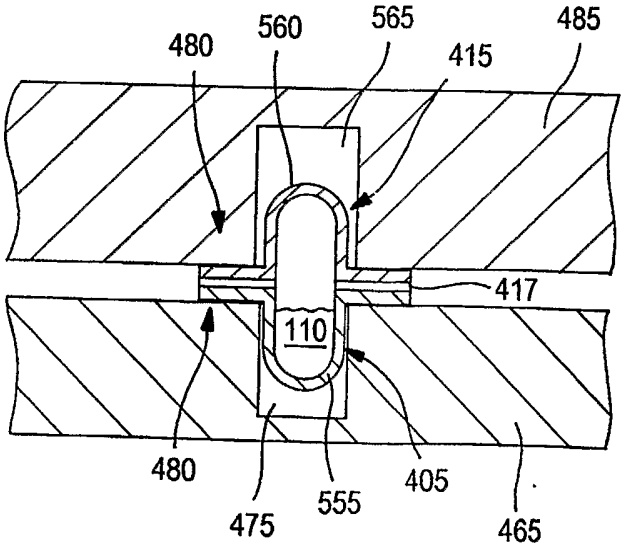

100
115
105
400
415
417
110
550
405

FIG. 13


480
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565
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415
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555
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465

FIG. 14

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 02/39058

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 B65D81/24 B65D81/20

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 7 B65D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 560 490 A (CHAWLA) 1 October 1996 (1996-10-01) column 3, line 56 -column 4, line 4 column 4, line 38 - line 43; figures	1,7-9, 21,22
X	WO 95 01920 A (DALLAS BURSTON ASHBOURNE) 19 January 1995 (1995-01-19) page 5, paragraph 2; figures	1,21
X	US 4 429 792 A (MACHBITZ) 7 February 1984 (1984-02-07) column 4, line 15 - line 44; figures	1,3,7-9, 21,22
A		15,17
X	US 5 957 317 A (LEE) 28 September 1999 (1999-09-28) abstract; figures	1,5,13, 14

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 March 2003	03/04/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gino, C

INTERNATIONAL SEARCH REPORT

Inte ɔnal Application No
PCT/US 02/39058

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
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