

**MEDICAMENT VIAL HAVING A HEAT-SEALABLE CAP,
AND APPARATUS AND METHOD FOR FILLING THE VIAL**

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Field Of The Invention

The present invention relates to heat-sealable caps for medicament vials for use where a sterile medicament must be maintained following temporary introduction of a needle or syringe through the cap, and to apparatus and methods for filling such vials.

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Background Of The Invention

Medicaments such as vaccines are often stored in vials prior to use. Typically, the vials are filled with medicament, and then a cap is installed to seal the medicament in the vial. The cap is typically made of vulcanized rubber or similar resilient material that neither contaminates nor affects the contained medicament.

15 One of the drawbacks associated with this type of filling procedure is that it is difficult to maintain the sterility of the cap during the assembly procedure. In

addition, it is difficult to maintain the sterility of the vials and caps during transportation and storage prior to filling.

In order to overcome this contamination risk, the present inventor has determined that it would be desirable to first assemble the cap to the vial, sterilize
5 the assembled cap and vial, such as by irradiation, and then fill the assembled vial by inserting a needle or like injection member through the cap and introducing the medicament through the needle into the sterilized vial. One of the drawbacks associated with this approach, however, is that when the needle or like injection member is inserted through the cap and then withdrawn, it leaves a tiny hole in the
10 cap. The material of the cap is resilient in order to reduce the diameter of the hole, and therefore the hole is usually small enough to keep the medicament from leaking out. However, the hole typically is not small enough to prevent air or other gases from passing through the hole and into the vial, and therefore such holes can allow the medicament to become contaminated or spoiled.

15 It has been a practice in the pharmaceutical fields to add preservatives to medicaments, such as vaccines, in order to prevent spoilage of the medicaments upon exposure to air or other possible contaminants. Certain preservatives, however, have been determined to cause undesirable effects on patients. Consequently, many medicaments, including vaccines, are preservative free. These
20 preservative-free medicaments, and particularly preservative-free vaccines, are subject to contamination and/or spoilage if contained within a vial wherein the cap has a needle hole as described above.

Vulcanized rubber has been determined to be a safe and effective material for manufacturing vial caps for containing numerous types of medicaments. Many

other polymeric materials have not been tested for compatibility with such medicaments, and therefore cannot be used to replace the vulcanized rubber currently used to manufacture caps for medicament vials. Vulcanized rubber, however, is infusible, and therefore any needle holes in such caps are not heat-
5 resealable in situ.

Accordingly, it is an object of the present invention to overcome the above-described drawbacks and disadvantages of the prior art.

Summary Of The Invention

The present invention is directed to a resealable cap for a medicament vial
10 comprising a base portion formed of vulcanized rubber or like material known for providing a stable environment for the medicament contained within the vial, and a resealable portion overlying the base portion. The resealable portion is made of a resealable polymeric material, such as low-density polyethylene, and can be punctured by a needle or like injection member for dispensing medicament into the
15 vial. Upon removal of the needle, the punctured area of the resealable portion can then be heat sealed to maintain the chamber containing the medicament in a hermetically sealed condition.

The present invention is also directed to an apparatus and method for filling a resealable vial with a predetermined medicament. The method includes the steps of
20 providing a vial; a resealable cap including a base portion substantially infusible in response to the application of thermal energy thereto, wherein the resealable portion is compatible with the predetermined medicament for exposure to the medicament and for sealing the medicament within the vial; a resealable portion overlying the

base portion and being fusible in response to the application of thermal energy thereto; and a locking member engageable with the cap and vial for securing the cap to the vial. Prior to filling the vial with medicament, the resealable cap and locking member are secured to the vial to thereby form a substantially gas-tight seal between the cap and vial. Then, the assembled cap, vial and locking member are sterilized, such as by exposure to beta or gamma radiation. A needle or like injection member is then inserted through the resealable cap and the predetermined medicament is introduced through the needle and into the interior of the vial. In the preferred embodiment of the present invention, the needle is a "double lumen" needle defining a core passageway for the introduction of the predetermined medicament therethrough and into the vial, and an annular passageway coupled in fluid communication with a vacuum source for withdrawing displaced air or other gases or vapors from the interior of the vial. Upon filling the vial with medicament, the needle is withdrawn from the cap, and sufficient thermal energy is applied to the penetrated region of the resealable portion of the cap to fuse the penetrated region and form a substantially gas-tight seal between the penetrated region and the interior of the vial. Preferably, the penetrable region of the resealable member is cauterized, such as by direct heat cauterization or laser cauterization, prior to introducing the needle through the cap, to further ensure the maintenance of sterile conditions throughout the assembly and filling processes.

One advantage of the apparatus and method of the present invention, is that the caps and locking members are secured to the vials prior to filling, thus enhancing the ability to maintain sterile conditions throughout the filling process and avoiding the need to assemble the vials in a sterile environment. As a result, the apparatus

penetration region that is pierceable with a needle to form a needle aperture
therethrough, and is heat resealable to hermetically seal the needle aperture by
applying laser radiation from a laser source at a predetermined wavelength and
power thereto. The needle penetration region defines a predetermined color and
5 opacity that (i) substantially absorbs the laser radiation at the predetermined
wavelength and substantially prevents the passage of the radiation through the
predetermined wall thickness thereof, and (ii) causes the laser radiation at the
predetermined wavelength and power to hermetically seal the needle aperture
formed in the needle penetration region thereof in a predetermined time period. The
10 assembly further includes a filling machine including a needle for penetrating the
resealable stopper and introducing a substance through the stopper and into the
container, a substance source coupled in fluid communication to the needle for
introducing the substance through the needle and into the container, and a laser
source connectable in thermal communication with the resealable stopper for
15 applying laser radiation at the predetermined wavelength and power thereto.

One advantage of the apparatus and method of the present invention, is that
the caps and locking members are secured to the vials prior to filling, thus enhancing
the ability to maintain sterile conditions throughout the filling process and avoiding
the need to assemble the vials in a sterile environment. As a result, the apparatus

and method of the present invention significantly reduce processing time and cost in comparison to prior art vials and filling systems, and moreover, significantly increase the assurance of sterility throughout the assembly and filling processes.

Other advantages of the present invention will become readily apparent in
5 view of the following detailed description and accompanying drawings.

Brief Description Of The Drawings

FIG. 1 is a somewhat schematic, partly-exploded, cross-sectional view of a prior art end cap for a medicament vial.

10 FIG. 2 is a cross-sectional, partly-exploded view of a resealable cap embodying the present invention.

FIG. 3 is a cross-sectional, partly exploded view of the resealable cap of FIG. 2 shown with an injection needle or syringe inserted through the end cap for introducing medicament into the vial, and a venting needle or syringe inserted
15 through the end cap for venting the vial during filling of the medicament.

FIG. 4 is a cross-sectional view of another embodiment of the resealable cap and vial of the present invention.

FIG. 5 is a cross-sectional view of the crimpable locking member of FIG. 4 for securing the resealable cap to the vial.

20 FIG. 6 is a cross-sectional view of the base portion of the resealable cap of FIG. 4 made of a material compatible with the predetermined medicament to be sealed within the vial, such as vulcanized rubber.

FIG. 7 is a cross-sectional view of the resealable portion of the cap of FIG. 4 formed of a material that is fusible in response to the application of thermal energy

thereto in order to hermetically seal the cap after inserting and removing a filling needle or like instrument therethrough.

FIG. 8 is an enlarged, partial, cross-sectional view of the resealable portion of FIG. 7 and showing the penetrable portion thereof for receiving a needle or like
5 instrument therethrough.

FIGS. 9A through 9C are somewhat schematic, cross-sectional, sequential views illustrating the apparatus and method of the present invention for sterilizing the resealable portion of the cap by direct heat cauterization prior to introducing the filling needle or like instrument therethrough.

10 FIG. 10 is a somewhat schematic, partial cross-sectional view of an apparatus embodying the present invention for sterilizing the resealable portion of the cap by laser cauterization prior to introducing the filling needle or like instrument therethrough.

FIG. 11 is a somewhat schematic, partial cross-sectional view of an
15 apparatus embodying the present invention for needle filling the assembled cap, vial and locking member with a predetermined medicament.

FIGS. 12A through 12D are somewhat schematic, cross-sectional, sequential views illustrating the apparatus and method of the present invention for hermetically sealing the penetrated region of the resealable portion of the cap by direct heat
20 sealing after withdrawing the filling needle therefrom.

FIGS. 13A through 13C are somewhat schematic, cross-sectional, sequential views illustrating the apparatus and method of the present invention for hermetically sealing the penetrated region of the resealable portion of the cap by laser sealing after withdrawing the filling needle therefrom.

Detailed Description Of The Preferred Embodiments

As shown in FIG. 1, a prior art cap for a medicament vial is generally
5 designated by the reference numeral 10. The cap 10 includes a vulcanized rubber
base 12, which is slidably received within the open end of a vial 14. The vial 14 is
made of glass or like material, and it defines a chamber 16 for receiving
medicament. An aluminum locking ring 18 surrounds the periphery of the cap 12
and vial 14, and it is crimped in place to lockably connect and seal the cap to the
10 vial.

In operation, a hypodermic needle (not shown) is inserted through the
vulcanized rubber base in order to deposit medicament within the chamber 16. Once
the medicament has been deposited, the needle is withdrawn from the cap 10.
Although the hole resulting from insertion of the needle will shrink somewhat from
15 its maximum diameter due to the resiliency of the vulcanized rubber, the resultant
hole is typically still large enough to pass gas or vapor and thereby compromise any
preservative-free medicament contained within the chamber 16.

Turning to FIG. 2, a heat-resealable cap embodying the present invention is
indicated generally by the reference numeral 110. The cap 110 includes a resilient
20 base 112 made of vulcanized rubber or like material which is known to those of
ordinary skill in the pertinent art, and acceptable for use in the manufacture of end
caps or the portions thereof placed in contact with, or otherwise exposed to
medicaments, such as vaccines. The base 112 defines a lower peripheral wall 115
shaped and dimensioned to be slidably received within the open end of a vial 114.
25 The vial 114 is made of glass or like material, and it defines a chamber 116 for

receiving medicament. The base 112 of the cap 110 further defines an upper peripheral wall 117 also shaped and dimensioned to be slidably received within the open end of the vial 114, and a peripheral sealing flange 118 projecting outwardly from the upper end of the peripheral wall 117. The vial 114 is made of glass or other suitable material, and defines at its open end a peripheral flange 120. As shown partly-exploded in FIGS. 2 and 3, the peripheral flange 118 of the base 112 sealingly engages the peripheral flange 120 of the vial 114 to seal the interface between the cap and vial. The base 112 further defines an upper recess 122 formed within the upper peripheral wall 117, and an annular rim 124 projecting inwardly from the upper end of the peripheral wall.

A resealable member 126 is fixedly received within the upper recess 122 of the base 112 to form the assembled cap 110. The resealable member 126 defines an upper peripheral flange 128, an annular recessed portion or recess 130, and a base 132 located on the opposite side of the annular recess 130 relative to the flange, and projecting outwardly from the recess. As can be seen in FIGS. 2 and 3, the annular recess 130 and base 132 of the resealable member 126 are dimensioned and shaped complementary to (or define the mirror image of) the interior surfaces of the upper recess 122 and annular rim 124 of the base 112. Accordingly, the resealable member 126 is pressed, snapped or otherwise received within the upper recess 122 such that the annular rim 124 is received within the annular recess 130 to thereby fixedly secure the resealable member within the base.

The resealable member 126 is preferably made of a resilient polymeric material, such as a blend of the polymeric material sold by Kraton Polymers and GLS Corporation under the registered trademark KRATON® and a low-density polyethylene, such as the

polyethylene sold by Dow Chemical Co. under the trademarks ENGAGE™ or EXACT™. An important feature of the resealable member 126 is that it be resealable to form a gas-tight seal after inserting a needle, syringe or like injection member through the resealable member. Preferably, the resealable member can be sealed by heating the area
5 punctured by the needle in a manner known to those skilled in the pertinent art and described further below. One advantage of the blended polymer described above is that it is known to minimize the degree to which the medicament can be absorbed into the polymer in comparison to KRATON® itself.

An aluminum locking or crimping ring 134 defining an upper peripheral
10 flange 136 and a lower peripheral flange 138 is mounted over the end cap 110 and vial 114. The locking ring 134 is of a type known to those of ordinary skill in the pertinent art for fixedly securing end caps to vials, and may take the shape or form of any of numerous different locking rings which are currently or later become known for performing the functions of the locking ring described herein. The upper
15 and lower flanges 136 and 138, respectively, of the locking ring are crimped or otherwise pressed against the adjacent surfaces of the cap and vial to press the sealing flanges of the cap against the vial and thereby maintain a fluid-tight and/or gas-tight seal between the cap and vial.

As shown in FIG. 3, the heat-resealable cap 110 is shown with a hypodermic
20 or other type of needle 140 inserted through the resealable member 126 and the resilient base 112 in order to dispense medicament into the chamber 116 of the vial. A venting needle 142 is likewise inserted through the resealable member 126 and the resilient base 112 in order to allow gas to escape from the vial 114 as the medicament is deposited into the vial. Preferably, the apparatus and method for

medicament is deposited into the vial. Preferably, the apparatus and method for dispensing the medicament into the vial is as shown in U.S. Patent No. 5,641,004 to Daniel Py, issued June 24, 1997, which is hereby expressly incorporated by reference as part of the present disclosure.

5 In operation, the resealable member 126 is inserted into the base 112, and the assembled end cap 110 is slidably inserted into the open end of the vial 114. The locking ring 134 is then crimped in place to lock the cap 110 to the vial and maintain the gas-tight seal at the interface of the cap and vial. The assembled cap 110 and vial 114 preferably are then sterilized, such as by exposing the assembly to beta
10 and/or gamma radiation in a manner known to those of ordinary skill in the pertinent art. The medicament-dispensing needle 140 is then inserted through the resealable member 126 and the resilient base 112 until the free end of the needle is received into the chamber 116 of the vial to, in turn, dispense medicament into the chamber. The venting needle 142 is likewise inserted through the resealable member 126 and
15 the resilient base 112 in order to draw gas from the sealed vial as the liquid medicament is deposited within the chamber of the vial. Once the medicament has been deposited within the chamber of the vial, the needles 140 and 142 are withdrawn from the cap 110, and as described further below, a heat or other energy source is applied to the portions of the resealable member 126 punctured by the
20 needles 140 and 142 to, in turn, seal the punctured areas and hermetically seal the medicament within the vial.

One advantage of the preferred embodiments of the present invention is that the resealable member 126 of the cap 110 may be resealed following the deposit of medicament into the chamber 116, thereby rendering the end cap of the invention

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particularly suitable for use with preservative-free medicaments, such as preservative-free vaccines. Accordingly, a further advantage of the preferred embodiments of the present invention is that the medicament need not contain a preservative, and therefore the above-described drawbacks and disadvantages of such preservatives can be avoided.

Another advantage of the preferred embodiments of the present invention is that the medicament within the resealed chamber 116 is not contaminated or otherwise affected by impurities or other agents in the atmosphere where the vial is stored or transported.

In FIGS. 4 through 8 another resealable cap embodying the present invention is indicated generally by the reference numeral 210. The resealable cap 210 is essentially the same as the cap 110 described above, and therefore like reference numerals preceded by the numeral "2" instead of the numeral "1" are used to indicate like elements. As shown best in FIGS. 4 and 6, the base 212 of the cap defines on the interior side of its upper peripheral wall 217 an annular groove 230. As shown best in FIGS. 4 and 7, the resealable member 226 defines on the peripheral surface of its base 232 an annular raised portion or protuberance 224 dimensioned to be frictionally received within the corresponding annular groove 230 of the base 212 to thereby secure the resealable member to the base. As shown in FIG. 6, the base 212 further defines on the exterior side of its lower peripheral wall 215 a plurality of raised annular portions or protuberances 244 axially spaced relative to each other for frictionally engaging the interior wall of the vial 214 to thereby secure the cap within the vial and facilitate maintaining a hermetic seal between the cap and vial. As shown best in FIGS. 7 and 8, the resealable member

226 defines on its top surface an annular raised portion or protuberance 246 defining a circular surface portion 248 therein for receiving a filling needle or like instrument, as described further below. As shown in FIG. 5, the locking or crimping ring 234 defines a central aperture 250 in its upper side for receiving therethrough the annular raised portion 246 of the resealable member 226.

Preferably, the resealable cap 210 and vial 214 are assembled and the locking ring 234 is crimped in place as described above and shown in FIG. 4 prior to introducing any medicament or other fluid into the vial. Then, one or more of the empty cap/vial assemblies of the present invention are enclosed, sterilized, and transported in accordance with the teachings of the present inventor's commonly owned U.S. Patent No. 5,186,772, entitled "Method Of Transferring Articles, Transfer Pocket And Enclosure", which is hereby expressly incorporated by reference as part of the present disclosure. As disclosed in the '772 patent, the empty cap/vial assemblies are placed in an internal bag or "pocket" which is closed and, if desired, provided with a sterilization indicator. Then, the internal pocket is placed within a transfer pocket including a sealing frame defining an annular groove on a peripheral surface thereof. The transfer pocket is stretched over the surface of the frame and closed by an elastic band overlying the transfer pocket and received within the peripheral groove. The transfer pocket likewise may include therein a sterilization indicator. Preferably, the assembled transfer and internal pockets are sealed within an "external" pocket and the assembled pockets are subject to sterilization, such as by exposure to gamma radiation, to sterilize the pockets and the empty cap/vial assemblies within the pockets. The transfer pockets can then be used to store and/or transport the sterilized assemblies to a filling system without

contaminating the sterilized assemblies. As further described in the '772 patent, the filling system is located within a sterile enclosure, and the empty vials are introduced into the enclosure by removing and discarding the external pocket, and connecting the sealing frame of the transfer pocket to a window or transfer port of the enclosure. As further disclosed in the '772 patent, an adhesive material is preferably superimposed on the sealing frame for securing the transfer pocket to the transfer port of the filling system enclosure. Prior to releasing the cap/vial assemblies into the filling system enclosure, the sterilization indicators are preferably checked in order to ensure that the sterile condition of the vial/cap assemblies were maintained throughout storage and transfer. As described in the '772 patent, the portion of the transfer pocket overlying the frame is then cut away and simultaneously sterilized along the trimmed surfaces to destroy any microorganisms or germs thereon, and to allow the internal pocket to be received through the transfer port and into the enclosure.

Once received within the enclosure, the internal pocket is opened and the empty cap/vial assemblies are removed and loaded into a filling machine located within the sterile enclosure. Once loaded into the filling machine, the resealable member 226 of each empty cap/vial assembly is preferably sterilized again in order to further ensure that no contaminants enter the vial during the filling process. In accordance with the preferred embodiments of the present invention, the resealable members 226 are sterilized at this stage by either direct heat cauterization or laser cauterization.

As shown in FIGS. 9A through 9C, an apparatus for cauterizing the resealable caps by application of heat thereto is indicated generally by the reference

numeral 252. The apparatus 252 comprises a housing 254 mounted over a vial support 256. The vial support 256 may be adapted to hold a single vial, or preferably, is adapted hold a plurality of vials. The embodiment of the support adapted to hold a plurality of vials defines a channel 258 for receiving therein the
5 vials, and a pair of opposing shoulders 260 formed at the upper edge of the channel for supporting thereon the flange 220 of the vial. If desired, a vibratory drive (not shown) may be drivingly connected to the support 256 to vibrate the support and, in turn, move the vials through the channel at a predetermined rate. However, as may be recognized by those skilled in the pertinent art based on the teachings herein, any
10 of numerous different drive systems that are currently, or later become known, may be equally employed to move the vials through the filling machine.

The housing 254 defines a peripheral sealing surface 262 formed on the free end of the housing for sealingly engaging the upper flange surface 236 of each locking member 234. As shown best in FIG. 9B, the peripheral sealing surface
15 surrounds the aperture 250 formed through the locking member and exposing the penetrable region 248 of the resealable member 226 of the cap. Preferably, the peripheral sealing surface 262 forms a substantially fluid-tight seal between the housing and the cap. A heating surface 264 projects outwardly from the free end of a central support 266 of the housing for contacting the penetrable surface 248 of the
20 resealable member and cauterizing the surface. An annular conduit 268 extends about the periphery of the heating surface 264 and is coupled in fluid communication to a vacuum source 270 for drawing air through the conduit and away from the cauterized surface 248, as indicated by the arrows in the Figures. The housing 254 is drivingly connected to a drive source 272 for moving the housing and

thus the heating surface 264 into and out of engagement with the exposed penetrable surface portion 248 for cauterizing the surface, as indicated by the arrows in the Figures. As may be recognized by those skilled in the pertinent art based on the teachings herein, the drive source 272 may take the form of any of numerous
5 different types of drive sources that are currently, or later become known, for performing the function of the drive source as described herein, such as a pneumatic drive, or a solenoid-actuated or other type of electric drive. Similarly, the heating surface 264 may take any of numerous different shapes and configurations, and may be heated in any of numerous different ways that are currently or later become
10 known, such as by an electric resistance heater (or "hot wire"). Preferably, however, the heating surface 264 defines a surface shape and contour corresponding to the desired shape and contour of the penetrable surface region 248 of the cap.

In the operation of the apparatus 252, and as shown typically in FIG. 9A, each vial is first introduced into the cauterizing station with the penetrable surface
15 region 248 of the resealable member 226 aligned with the heating surface 264. Then, the drive source 272 is actuated to drive the housing 254 downwardly until the peripheral sealing surfaces 262 sealingly engage the upper flange surface 236 of the respective locking member 234, and the heating surface 264 simultaneously engages the exposed penetrable surface portion 248 of the resealable member 226. The
20 heated surface 264 is maintained at a predetermined temperature, and is held in contact with the exposed surface portion 248 for a predetermined time period, sufficient to cauterize the exposed surface portion. One advantage of the construction of the resealable member 226 as shown in FIGS. 7 and 8, is that the cauterization process deforms the annular protuberance 246 into a contour

conforming to that of the heated surface, thus allowing an operator (or optical or other automatic sensing system) to visually determine whether each cap has been properly cauterized prior to filling. As shown in FIG. 9C, after cauterizing the exposed surface, the drive source 272 is actuated to drive the housing 254 upwardly and out of engagement with the cap, another vial is moved under the housing, and the process is repeated until all desired vials are cauterized. As described further below, upon exiting the cauterizing station of FIGS. 9A through 9C, the vials are preferably then moved into a filling station to promptly fill the sterilized vials. The cauterization and filling stations are preferably mounted within a sterile enclosure with a laminar gas flow through the enclosure to facilitate maintaining the sterile conditions, as described, for example, the above-mentioned '772 patent.

In the currently preferred embodiment of the present invention, the temperature of the heating surface is within the range of approximately 250° C to 300° C, and the cycle times (i.e., the time period during which the heating surface is maintained in contact with the exposed surface 248 of the resealable member) are within the range of approximately 1.0 to 3.0 seconds. The present inventor has determined that these temperatures and cycle times may achieve at least approximately a 6 log reduction in bio-burden testing to thereby effectively sterilize the surface.

In FIG. 10, an alternative apparatus for cauterizing the resealable caps is indicated generally by the reference numeral 274. The apparatus 274 differs from the apparatus 252 of FIGS. 9A through 9C in that the thermal energy required for sterilizing the filling area of the resealable member is supplied by a laser (referred to herein as "laser cauterization"). The laser cauterization apparatus 274 comprises a

laser or other suitable radiation source 276 optically coupled to a scanning mirror 278 mounted over the vial/cap assembly. Although not shown in FIG. 10, the vials are preferably mounted within the same type of support as shown in FIGS. 9A through 9C in order to allow the resealable caps to be rapidly cauterized in succession prior to filling each vial with medicament, as described further below.

In the currently preferred embodiment of the present invention, the laser 276 is a commercially available CO₂ or YAG laser. The CO₂ laser operates at a wavelength of approximately 10.6 μm . At this wavelength, absorption of the laser energy is governed by the electrical conductivity of the material. Therefore, an insulating material, such as the elastomeric material of the resealable member 226, absorbs and converts most of the incident energy into thermal energy to cauterize the receiving surface 248. The YAG laser operates at wavelength of approximately 1.06 μm . At this frequency, absorption is governed by the lattice atoms. Thus, a clear or transparent polymer with little ionization would be permeable to the laser beam. Accordingly, when employing a YAG laser, it is desirable to add a colorant to the elastomeric material of the resealable member in a manner known to those of ordinary skill in the pertinent art in order to enhance its absorption of the laser energy. A significant advantage of the YAG laser is that the superficial layer of the penetrable region of the resealable member, and any germs, bacteria or other contaminants thereon, are transformed into plasma to rapidly and thoroughly sterilize the effected surface. If necessary, a UV-filtration coating may be applied to the surfaces of the enclosure for the apparatus of the invention to prevent the operators from receiving any unnecessary UV exposure.

The present inventor has demonstrated that beam energies in the range of approximately 15 to 30 W are sufficient to effectively cauterize the surface 248 of the elastomeric resealable member. In addition, bio-burden testing has demonstrated that laser energies of approximately 20W or greater may achieve a 6.0 log reduction.

5 At these energies, the apparatus of the present invention may effectively sterilize the surface 248 within a cycle time of approximately 0.5 seconds. Accordingly, a significant advantage of the laser cauterization apparatus and method of the present invention is that they may involve significantly shorter cycle times than various direct heat methods. Yet another advantage of the laser cauterization of the present
10 invention, is that it involves both a non-contact method and apparatus, and therefore there is no need to be concerned with the cleaning of a contact head or like heating surface.

Turning to FIG. 11, after direct heat or laser cauterization of the resealable member 226 of each vial, the vial is moved within the support 256 (such as by
15 vibratory drive) into a filling station 280. The filling station 280 includes a needle or like injection member 282 reciprocally mounted over the support 256, as indicated by the arrows in FIG. 11, and axially aligned with the penetrable region 248 of the resealable member 226 of each vial/cap assembly passing therethrough. A drive source 284 is drivingly connected to the needle 280 for reciprocally driving
20 the needle 282 into and out of engagement with each cap 210. A medicament or other formulation reservoir 286 is coupled in fluid communication with the needle 282 for introducing a predetermined medicament or other formulation through the needle and into the vial. In the currently preferred embodiment of the present invention, the needle 282 defines a plurality of fluid conduits therein, including a

first fluid conduit 288 for injecting the predetermined medicament or other formulation into the vial, as indicated by the arrow in FIG. 11, and a second fluid conduit 290 coupled in fluid communication with a vacuum source 292 for withdrawing air or other gases from the interior cavity 216 of the vial prior to and/or during the filling of the cavity with the medicament or other formulation. In the illustrated embodiment of the present invention, the needle 282 is a "double lumen" needle, defining a central fluid conduit 288 for injecting the predetermined medicament or other formulation into the vial, and an outer annular fluid conduit 290 for drawing the displaced air or other gases out of the interior cavity of the vial.

As shown in FIGS. 12A through 12D, after filling the vial with the medicament or other formulation and withdrawing the needle 282 from the cap 210, the penetrated region of the cap defines a needle hole 294 along the path of the withdrawn needle (FIG. 12B). Upon withdrawing the needle, the vulcanized rubber base 212 of the cap is sufficiently resilient to close upon itself in the penetrated region and thereby maintain the vial in a sealed condition. However, as described above, vapors, gases and/or liquid may be allowed over time to pass through the needle hole, and therefore each vial/cap assembly is passed through a sealing station, as shown typically in FIG. 12C, to heat seal the resealable portion 226 of the cap promptly after withdrawing the needle therefrom. As shown typically in FIG. 12C, a heated member or surface 264 is reciprocally mounted over, and axially aligned with the penetrable region 248 of the vial/cap assembly received within the filling station. A drive source 272 is drivingly connected to the heated member 264 to reciprocally drive the heated member into and out of engagement with the resealable member of each cap. As shown typically in FIG. 12C, the heated member 264 is

maintained at a sufficient temperature, and maintained in engagement with the penetrated region of the resealable member 226 to fuse the elastomeric material and hermetically seal the needle hole 294. As a result, and as shown typically in FIG. 12D, the needle hole is eliminated from the exterior region of the resealable member
5 to thereby maintain a hermetic seal between the cap and vial.

As may be recognized by those skilled in the pertinent art based on the teachings herein, the drive source and heating member/surface of FIGS. 12A through 12D may take the form of any of numerous different drive sources and heating members as described above. As indicated typically in FIG. 12C, however,
10 the heating member 264 may define a smaller width than the heating member/surface described above for cauterizing the penetrable region of the cap prior to filling. In addition, the temperature of the heating member 264 for sealing may be higher than that of the heating member described above in order to rapidly melt and seal the penetrated region. One advantage of the resealable cap of the
15 present invention, is that the underlying rubber base 212 thermally insulates the heated region from the medicament in the vial to thereby maintain the medicament in the vial within an appropriate temperature range throughout the cauterization and heat sealing processes and thereby avoid any thermal damage to the medicament.

Alternatively, and as shown in FIGS. 13A through 13C, the laser source 276
20 and scanning mirror 278 may be employed to heat seal the penetrated region 294/248 of the resealable member. Accordingly, the same type of laser source 276 and scanning mirror 278 as described above may be employed in the heat sealing station to perform this function, or alternatively, a different type of laser system may be employed. In a currently preferred embodiment of the present invention, a CO₂

laser of approximately 50 W is employed to seal a region approximately 0.10 inch in diameter in the resealable cap.

As may be recognized by those skilled in the pertinent art based on the teachings herein, numerous changes and modifications may be made to the above-described and other embodiments of the present invention without departing from its scope as defined in the appended claims. For example, the resealable member may be integrally molded with the base such as by insert molding, the resealable member may be fused or otherwise melted to the base, or the resealable member may be sequentially molded to the base. In addition, the resealable member may be made of any of numerous different materials which are currently known, or which later become known for performing the functions of the resealable member described herein, such as any of numerous different thermoplastic and/or elastomeric materials, including, for example, low-density polyethylene. Similarly, the base can be made of vulcanized rubber as described above, or any of numerous other materials which are currently, or later become known as being compatible with, or otherwise defining a stable enclosure for the particular medicament contained within the vial. In addition, the end cap of the invention may include more than one layer of vulcanized rubber and/or more than one layer of resealable material. In addition, the cauterization and sealing stations of the present invention may employ any of numerous different types of heat sources that are currently, or later become known, for performing the functions of the heat sources described herein, such as any of numerous different types of laser or other optical sources or conductive heat sources. Accordingly, this detailed description of the preferred embodiments is to be taken in an illustrative, as opposed to a limiting sense.

What is claimed is:

1. A resealable stopper for sealing a predetermined substance within a container including a locking member securing the stopper to the container, wherein the container is usable in a filling assembly including a filling member for penetrating the resealable stopper and introducing the substance through the stopper and into the container, a substance source coupled in fluid communication to the filling member for introducing the substance through the filling member and into the container, and at least one thermal energy source connectable in thermal communication with the resealable stopper, wherein the resealable stopper comprises:

a base portion formed of a first material compatible with the predetermined substance within the container, the base portion defining a peripheral surface for contacting an open end of the container and a substance-exposed surface defining the portion of the stopper exposed to the predetermined substance contained within the container; and

a resealable portion overlying the base portion, the resealable portion and base portion being penetrable by the filling member for introducing the predetermined substance through the stopper and into the container, wherein the penetrable region of the base portion is substantially infusible in response to the application of thermal energy from the thermal energy source thereto, and the penetrable region of the resealable portion is fusible in response to the application of thermal energy from the thermal energy source thereto to form a gas-tight seal between the resealable portion and the substance in the container upon removing the filling member therefrom.

2. A resealable stopper as defined in claim 1, wherein the resealable portion is formed of at least one of a thermoplastic and elastomeric material.

3. A resealable stopper as defined in claim 1, wherein the base portion is formed of vulcanized rubber.

4. A resealable stopper as defined in claim 1, in further combination with a locking member engageable with the stopper and container for securing the stopper to the container.

5. A resealable stopper and locking member as defined in claim 4, wherein the locking member defines at least one peripheral flange crimpable to the stopper and container for securing the stopper to the container.

6. A resealable stopper as defined in claim 1, wherein the base portion defines an interior cavity, and the resealable portion is received within the interior cavity of the base portion.

7. A resealable stopper as defined in claim 6, wherein one of the base and resealable portions defines at least one recessed surface area, and the other of the base and resealable portions defines at least one raised surface area, and wherein each raised surface area is received within a corresponding recessed surface area for securing the resealable portion to the base portion.

8. A resealable stopper as defined in claim 7, wherein at least one raised surface area is in the form of an annular protuberance, and at least one recessed surface area is in the form of a corresponding annular groove for receiving the annular protuberance.

9. A stopper as defined in claim 1, wherein the substance is a medicament.

10. A stopper as defined in claim 1, wherein the container is a vial.

11. A stopper as defined in claim 1, wherein the filling member is a needle.

12. An assembly, comprising:

a vial;

a resealable cap for sealing a predetermined substance within the vial, wherein the resealable cap includes:

a base portion formed of a first material compatible with the predetermined substance within the vial, the base portion defining a peripheral surface for contacting an open end of the vial and a substance-exposed surface defining the portion of the cap exposed to the predetermined substance contained within the vial;

a resealable portion overlying the base portion, the resealable portion and base portion being penetrable by a filling member for introducing the predetermined substance through the cap and into the vial, wherein the penetrable region of the base portion is substantially infusible in response to the application of thermal energy thereto, and the penetrable region of the resealable portion is fusible in response to the application of thermal energy thereto for hermetically sealing the penetrable region upon removing the filling member therefrom;

a locking member engaging the cap and vial and securing the cap to the vial; and
a filling assembly, including:

a filling member for penetrating the resealable cap and introducing the predetermined substance through the cap and into the vial;

a substance source coupled in fluid communication to the filling member for introducing the substance through the filling member and into the vial; and

at least one thermal energy source coupled in thermal communication with the resealable cap for applying thermal energy to the region of the resealable portion penetrable by the filling member and fusing the penetrable region to form a gas-tight seal between the resealable portion and the substance in the vial.

13. An assembly as defined in claim 12, wherein the filling member defines a first fluid passageway coupled in fluid communication with the substance source for introducing the substance therethrough and into the container, and a second fluid passageway extending adjacent to the first fluid passageway and coupled in fluid communication with a vacuum source for drawing displaced gas out of the container upon introducing the substance therein.

14. An assembly as defined in claim 12, wherein the at least one thermal energy source includes a laser directed onto the penetrable region of the resealable portion for transmitting radiation thereon and fusing the penetrable region to form a gas-tight seal.

15. An assembly as defined in claim 12, wherein the filling assembly includes a heating assembly forming the thermal energy source, the heating assembly includes a heated surface, and at least one of the heated surface and the resealable portion is movable relative to the other for engaging the resealable portion with the heated surface and fusing the penetrable region to form the gas-tight seal.

16. An assembly as defined in claim 15, wherein the filling assembly further includes a drive source drivingly connected to the heating assembly for moving the heated surface into and out of engagement with the penetrable region of the resealable portion.

17. An assembly as defined in claim 15, wherein the heating assembly includes:
a housing enclosing the heated surface and defining a peripheral sealing surface extending about the heated surface and engageable with the locking member for forming a seal between the housing and locking member;

at least one fluid conduit formed between the heated surface and the peripheral sealing surface; and

a vacuum source coupled in fluid communication with the at least one fluid conduit for drawing air away from the resealable portion upon moving the heated surface in contact therewith.

18. An assembly as defined in claim 17, wherein the at least one fluid conduit defines an annular passageway extending about the periphery of the heated surface.

19. An assembly as defined in claim 17, wherein the locking member defines an aperture exposing the resealable portion therethrough, and the heated surface projects outwardly beyond the peripheral sealing surface for engaging the resealable portion through the aperture upon engaging the locking member with the peripheral sealing surface.

20. A resealable stopper for sealing a predetermined substance within a container including a locking member securing the stopper to the container, wherein the container is usable in a filling assembly including a filling member for penetrating the resealable stopper and introducing the substance through the stopper and into the container, a substance source coupled in fluid communication to the filling member for introducing the substance through the filling member and into the container, and a thermal energy source connectable in thermal communication with the resealable stopper, wherein the resealable stopper comprises:

first means substantially infusible in response to an application of thermal energy from the thermal energy source thereto and compatible with the predetermined substance

in the container for exposure to the substance and for sealing the substance within the container; and

second means overlying the first means and fusible in response to the application of thermal energy from the thermal energy source thereto for forming a substantially gas-tight seal between the stopper and the interior of the container in a region thereof penetrable by the filling member.

21. A resealable stopper as defined in claim 20, wherein the first means is defined by an underlying portion of the stopper formed of vulcanized rubber.

22. A resealable stopper as defined in claim 20, wherein the second means is defined by a penetration region of the stopper formed of a thermoplastic.

23. A resealable stopper as defined in claim 20, in further combination with third means engageable with the stopper and container for securing the stopper to the container.

24. A resealable stopper as defined in claim 20, wherein the first means defines an interior cavity, and the second means is received within the interior cavity of the first means.

25. A resealable stopper as defined in claim 24, wherein one of the first and second means defines at least one recessed surface area, and the other of the first and second means defines at least one raised surface area, and wherein each raised surface area is received within a corresponding recessed surface area for securing the first means to the second means.

26. An assembly, comprising:

a vial;

a resealable cap for sealing a predetermined substance within the vial and capable of being penetrated for introducing the predetermined substance into the vial, wherein the resealable cap includes:

first means substantially infusible in response to an application of thermal energy thereto and compatible with the predetermined substance in the vial for exposure to the substance and for sealing the substance within the vial; and

second means overlying the first means and fusible in response to the application of thermal energy thereto for forming a substantially gas-tight seal between the cap and the interior of the vial in a penetrated region thereof;

third means engaging the cap and vial for securing the cap to the vial; and
a filling assembly, including:

fourth means for penetrating the resealable cap and introducing a substance through the cap and into the vial;

a substance source coupled in fluid communication to the fourth means for introducing the substance through the fourth means and into the vial; and

fifth means coupled in thermal communication with the first means for applying thermal energy to the region of the first means penetrable by the fourth means and fusing the penetrable region to form a gas-tight seal between the first means and the substance in the vial.

27. An assembly as defined in claim 26, wherein the fourth means defines a first fluid passageway coupled in fluid communication with the substance source for introducing the substance therethrough and into the vial, and a second fluid passageway extending adjacent to the first fluid passageway and coupled in fluid communication with a vacuum source for drawing displaced gas out of the vial upon introducing the substance therein.

28. A stopper as defined in claim 20, wherein the filling member is a needle.

29. A stopper as defined in claim 20, wherein the container is a vial.

30. A stopper as defined in claim 20, wherein the substance is a medicament.

31. An assembly, comprising:

a container;

a resealable stopper for sealing a predetermined substance within the container, wherein the resealable stopper includes:

a body defining a predetermined wall thickness in an axial direction thereof, a needle penetration region that is pierceable with a needle to form a needle aperture therethrough, and is heat resealable to hermetically seal the needle aperture by applying

laser radiation from a laser source at a predetermined wavelength and power thereto, wherein the needle penetration region defines a predetermined color and opacity that (i) substantially absorbs the laser radiation at the predetermined wavelength and substantially prevents the passage of the radiation through the predetermined wall thickness thereof, and (ii) that causes the laser radiation at the predetermined wavelength and power to hermetically seal the needle aperture formed in the needle penetration region thereof in a predetermined time period;

a locking member securing the stopper to the container;

a filling assembly including a needle for penetrating the resealable stopper and introducing

a substance through the stopper and into the container;

a substance source coupled in fluid communication to the needle for introducing the substance through the needle and into the container; and

a laser source connectable in thermal communication with the resealable stopper for applying laser radiation at the predetermined wavelength and power thereto.

32. An assembly as defined in claim 31, wherein the container is a vial.

33. An assembly as defined in claim 31, wherein the substance is a medicament.

34. An assembly as defined in claim 31, wherein the body further defines an underlying portion formed of a first material compatible with the predetermined substance within the container and defining a substance-exposed surface exposed to the predetermined substance contained within the container; and a resealable portion overlying the underlying portion, the resealable portion and underlying portion being penetrable by the needle for introducing the predetermined substance through the stopper and into the container, wherein the penetrable region of the underlying portion is substantially infusible in response to the application of thermal energy from the laser source, and the penetrable region of the resealable portion is fusible in response to the application of thermal energy from the laser source to form a gas-tight seal between the resealable portion and the substance in the container upon removing the needle therefrom.

35. An assembly as defined in claim 31, further comprising means for insulating the substance in the container from laser energy applied by the laser source to avoid thermal damage to the substance.

36. An assembly as defined in claim 35, wherein the means for insulating is defined by the body of the stopper.

37. An assembly as defined in claim 31, further comprising a radiation source for sterilizing the needle penetration region of the stopper prior to penetration thereof by the needle.

38. An assembly as defined in claim 37, wherein the radiation source is a laser source.

39. An assembly as defined in claim 38, wherein said laser source is capable of achieving an approximately 6 log reduction in bio-burden on the needle penetration region of the stopper.

40. An assembly as defined in claim 38, wherein said laser source sterilizes the needle penetration region within a cycle time of approximately 0.5 seconds.

41. An assembly as defined in claim 31, further comprising a first fluid passageway extending through the needle for introducing the substance from the substance source through the needle and into the container, and a second fluid passageway for allowing fluid to flow out of the container upon introducing the substance from the first fluid passageway into the container.

42. An assembly as defined in claim 41, wherein the second fluid passageway is defined by the needle.

43. An assembly as defined in claim 31, wherein the locking member extends about a peripheral portion of the stopper.

44. An assembly as defined in claim 31, wherein the substance source contains a preservative-free medicament, and the needle is adapted to introduce the preservative-free medicament through the stopper and into the container.

45. An assembly as defined in claim 31, wherein the needle is axially alignable with the needle penetration region of the stopper for penetrating the stopper and introducing the predetermined substance into the container.

46. An assembly as defined in claim 31, further comprising a sealed, empty container ready for filling in the filling assembly, wherein the sealed, empty container defines an opening, a resealable stopper covering the opening, and a locking member securing the stopper to the container.

47. An assembly as defined in claim 46, wherein the sealed, empty container is sterilized by the application of radiation thereto.

48. An assembly as defined in claim 46, further comprising a radiation source for sterilizing the sealed, empty container prior to filling with the predetermined substance.

49. An assembly as defined in claim 31, wherein the radiation source is a laser source for transmitting radiation at a predetermined wavelength and power onto the penetration region of the stopper of a sealed, empty container for a predetermined cycle time to sterilize a surface of the needle penetration region of the stopper prior to introducing the needle therethrough.

50. An assembly as defined in claim 49, wherein the predetermined cycle time is approximately 0.5 seconds.

51. An assembly as defined in claim 31, further comprising a container filled with the predetermined substance, wherein the filled container was previously a sealed, empty, sterilized container that was filled by penetrating the stopper with the needle and introducing the substance through the needle and into the container.

52. An assembly as defined in claim 51, wherein the filled container defines a resealed needle penetration region that was resealed by the application of laser radiation from the laser source thereto.

53. An assembly as defined in claim 52, wherein the filled container is filled with a preservative-free medicament.

54. A resealable stopper for sealing a predetermined substance within a container including a locking member for securing the stopper to the container, wherein the container is usable in a filling assembly including a needle for penetrating the resealable stopper and introducing a substance through the stopper and into the container, a substance source coupled in fluid communication with the needle for introducing the substance through the needle and into the container, and a laser source connectable in thermal communication with the resealable stopper, wherein the resealable stopper comprises:

a body defining a predetermined wall thickness in an axial direction thereof, a needle penetration region that is pierceable with the needle to form a needle aperture therethrough, and is heat resealable to hermetically seal the needle aperture by applying laser radiation from the laser source at a predetermined wavelength and power thereto, wherein the needle penetration region defines a predetermined color and opacity that (i) substantially absorbs the laser radiation at the predetermined wavelength and substantially prevents the passage of the radiation through the predetermined wall thickness thereof and (ii) that causes the laser radiation at the predetermined wavelength and power to hermetically seal the needle aperture formed in the needle penetration region thereof in a predetermined time period.

55. A stopper as defined in claim 54 in combination with a container and a locking member, wherein the container defines an opening, the resealable stopper covers the opening, and the locking member secures the stopper to the container.

56. A stopper as defined in claim 54, wherein the needle penetration region defines a relatively raised surface portion on an exterior surface of the stopper, and the body of the stopper defines a relatively recessed surface portion extending about a periphery of the relatively raised surface portion.

57. A stopper as defined in claim 54, wherein the substance is a medicament.

58. A stopper as defined in claim 54, wherein the container is a vial.

59. A stopper as defined in claim 54, wherein the body further defines an underlying portion formed of a first material compatible with the predetermined substance within the container and defining a substance-exposed surface exposed to the predetermined substance contained within the container; and a resealable portion overlying the underlying portion, the resealable portion and underlying portion being penetrable by the needle for introducing the predetermined substance through the stopper and into the container, wherein the penetrable region of the underlying portion is substantially infusible in response to the application of thermal energy from the laser source, and the penetrable region of the resealable portion is fusible in response to the application of thermal energy from the laser source to form a gas-tight seal between the resealable portion and the substance in the container upon removing the filling member therefrom.

60. A stopper as defined in claim 54, wherein the body insulates the substance in the container from laser energy applied by the laser source to avoid thermal damage to the substance.

61. The combination of a stopper, container and locking member as defined in claim 55 forming a sealed, empty container sterilized by the application of radiation thereto.

62. The combination of a stopper, container and locking member as defined in claim 55, further comprising a substance sealed within the container.

63. The combination of a stopper, container and locking member as defined in claim 55, wherein the substance is a preservative-free medicament.

64. An assembly, comprising:
a container;

a resealable stopper for sealing a predetermined substance within the container, wherein the resealable stopper comprises:

(i) a body defining a predetermined wall thickness in an axial direction thereof, wherein the body defines a needle penetration region that is pierceable with the needle to form a needle aperture therethrough, and is heat resealable to hermetically seal the needle aperture by applying laser radiation from a laser source at a predetermined wavelength and power thereto, (ii) first means for substantially absorbing laser radiation at the predetermined wavelength and substantially preventing the passage of the radiation through the predetermined wall thickness thereof, and (ii) second means for causing laser radiation at the predetermined wavelength and power to hermetically seal a needle aperture formed in the needle penetration region thereof in a predetermined time period;

a locking member securing the stopper to the container;

a filling assembly including a needle for penetrating the resealable stopper and introducing a substance through the stopper and into the container;

a substance source coupled in fluid communication to the needle for introducing the substance through the needle and into the container; and

a laser source connectable in thermal communication with the resealable stopper for applying laser radiation at the predetermined wavelength and power thereto.

65. An assembly as defined in claim 64, wherein the body insulates the substance in the container from laser energy applied by the laser source to avoid thermal damage to the substance.

66. An assembly as defined in claim 64, further comprising a radiation source for sterilizing the needle penetration region of the stopper prior to penetration thereof by the needle.

67. An assembly as defined in claim 66, wherein the radiation source is a laser source.

68. An assembly as defined in claim 67, wherein said laser source is capable of achieving an approximately 6 log reduction in bio-burden on the needle penetration region of the stopper.

69. An assembly as defined in claim 64, further comprising a first fluid passageway extending through the needle for introducing the substance from the substance source through the needle and into the container, and a second fluid passageway for allowing fluid to flow out of the container upon introducing the substance from the first fluid passageway into the container.

70. A resealable stopper for sealing a predetermined substance within a container including a locking member for securing the stopper to the container, wherein the container is usable in a filling assembly including an injection member for penetrating the resealable stopper and introducing the substance through the stopper and into the container, a substance source coupled in fluid communication with the injection member for introducing the substance through the injection member and into the container, and a laser source connectable in thermal communication with the resealable stopper, wherein the resealable stopper comprises:

(i) a body defining a predetermined wall thickness in an axial direction thereof, wherein the body defines a penetration region that is pierceable with the injection member to form an aperture therethrough, and is heat resealable to hermetically seal the aperture by applying laser radiation from the laser source at a predetermined wavelength and power thereto, (ii) first means for substantially absorbing laser radiation at the predetermined wavelength and substantially preventing the passage of radiation through the predetermined wall thickness thereof, and (ii) second means for causing laser radiation at the predetermined wavelength and power to hermetically seal an aperture formed by the injection member in the penetration region in a predetermined time period.

71. A stopper as defined in claim 70, wherein the first means is defined by the needle penetration region having a predetermined color and opacity that substantially absorbs laser radiation at the predetermined wavelength and substantially prevents the passage of said laser radiation through the predetermined wall thickness thereof.

72. A stopper as defined in claim 70, wherein the second means is defined by the needle penetration region having a predetermined color and opacity that causes laser radiation at the predetermined wavelength and power to hermetically seal a needle aperture formed in the needle penetration region thereof in a predetermined time period.

73. A stopper as defined in claim 70, wherein the predetermined wavelength is approximately 10.6 μm .

74. A stopper as defined in claim 70, wherein the predetermined wavelength is approximately 1.06 μm .

75. A stopper as defined in claim 70, wherein the predetermined power is within the range of approximately 15 to 30 Watts.

76. A stopper as defined in claim 70, wherein the body further defines first means substantially infusible in response to an application of thermal energy from the laser source and compatible with the predetermined substance in the container for exposure to the substance and for sealing the substance within the container; and second means overlying the first means and fusible in response to the application of thermal energy from the laser source for forming a substantially gas-tight seal between the stopper and the interior of the container.

77. A stopper as defined in claim 76, wherein the first means is defined by an underlying portion of the body formed of vulcanized rubber.

78. A stopper as defined in claim 76, wherein the second means is defined by a thermoplastic portion of the needle penetration region of the stopper.

79. A stopper as defined in claim 70, further comprising means for insulating the substance in the container from the laser energy to thereby avoid thermal damage to the substance.

80. A stopper as defined in claim 70 in combination with a container and a locking member, wherein the container defines an opening, the resealable stopper covers the

opening, and the locking member secures the stopper to the container, and further comprising a preservative-free medicament sealed within the container.