INJECTOR AND METHOD OF ASSEMBLY

Background

[0001] This patent is directed to an injector and a method of assembling the injector, and, in particular, to a prefilled injector and a method of assembling the prefilled injector.

[0002] Injectors are used to deliver medical fluids, such as liquid drugs, to a patient. In particular, the injector will provide the fluid to the patient through a needle, cannula or catheter that defines a flow path into the patient. Certain injectors have a reservoir that is assembled by the manufacturer already connected to the flow path. However, these reservoirs are typically provided empty by the manufacturer to the patient or healthcare provider (e.g., doctor, nurse, healthcare assistant, etc.), and then the reservoir is filled at the time of use. Alternatively, the injector may be used in combination with a reservoir that is provided to the patient or healthcare provider prefilled.

[0003] In either case, the injector must be prepared prior to use. For example, if the reservoir is provided empty, then the reservoir must be filled. To do this, a syringe is filled with the drug to be delivered, and then the drug is injected into the reservoir through an inlet port. Prior to the injection, the inlet port must be sterilized by swabbing the outer surface with an alcohol wipe, for example. Similarly, before the prefilled reservoir is connected to the flow path in the alternative injector, the mating connectors must be sterilized, by swabbing the surface with an alcohol wipe.

[0004] In either event, the use of the injector requires additional material and time.

[0005] As set forth in more detail below, the present disclosure sets forth an improved injector embodying advantageous alternatives to the conventional devices and methods discussed above.

Summary

[0006] According to an aspect of the present disclosure, an injector may include a container having a wall with an interior surface defining a closed sterile reservoir filled with a drug product. The injector may also include a sterile fluid delivery system which may or may not be in fluid communication with the sterile reservoir in a

storage state, but is in fluid communication with the reservoir in the delivery state. The injector further includes other clean elements (e.g., an actuator) that are assembled with the container and the needle.

[0007] The wall of the container may be a rigid wall or a flexible wall.

[0008] If the fluid delivery system is not in fluid communication in a storage state, the injector may include an actuator that is adapted to changes the state of the fluid delivery system from the storage state to the delivery state.

[0009] In such an injector, the actuator is adapted to change the state of the fluid delivery system repeatedly between the storage state and the delivery state.

[0010] In such an injector, the actuator may be adapted to delay change in state of the fluid delivery system from the storage state to the delivery state after an input is received.

[0011] In such an injector, the injector may include a mechanical, electro-mechanical, or electrical input device coupled to the actuator.

[0012] According to any of the foregoing, the drug product may include a volume of an erythropoiesis stimulating agent, a granulocyte colony-stimulating factor, a TNF blocker, a pegylated granulocyte colony-stimulating factor, interleukin-receptor specific antibody, IGF-receptor (Insulin Growth Factor receptor) specific antibody, TGF-specific antibody, or PCSK9 (Proprotein Convertase Subtilisin/Kexin Type 9) - specific antibody.

[0013] According to another aspect of the present disclosure, a method of assembling an injector may include filling a sterile reservoir of a container with a drug product under sterile conditions, the reservoir defined by an interior surface of a wall of the container. The method may also include attaching a sterile fluid delivery system to the container under sterile conditions to define a storage state in which the fluid delivery system may or may not be in fluid communication with the sterile reservoir, and a delivery state in which the fluid delivery system is in fluid communication. The method may include assembling the remainder of the injector under clean room conditions.

[0014] The method may also include attaching the fluid delivery system to an actuator under clean room conditions, the actuator adapted to change the state of the fluid delivery system from the storage state to a delivery state wherein the fluid

delivery system is in fluid communication with the container, and in particular the reservoir.

[0015] According to this aspect, the wall of the container may be a rigid wall or a flexible wall.

Brief Description of the Drawings

[0016] It is believed that the disclosure will be more fully understood from the following description taken in conjunction with the accompanying drawings. Some of the figures may have been simplified by the omission of selected elements for the purpose of more clearly showing other elements. Such omissions of elements in some figures are not necessarily indicative of the presence or absence of particular elements in any of the exemplary embodiments, except as may be explicitly delineated in the corresponding written description. None of the drawings are necessarily to scale.

[0017] Fig. 1 is a cross-sectional view of an embodiment of an injector according to the present disclosure, with a container needle in a storage state wherein the needle partially penetrates a unitary wall of the container;

[0018] Fig. 2 is a perspective view of a jig used with the container of the injector of Fig. 1 to control the penetration of the flexible unitary wall of the container by the container needle;

[0019] Fig. 3 is a cross-sectional view of the injector of Fig. 1, with the container needle in a delivery state wherein the needle penetrates the unitary wall of the container such that it is disposed through an interior surface of the flexible wall into a sterile reservoir;

[0020] Fig. 4 is a schematic of a manufacturing facility wherein injectors according to the present disclosure may be filled and assembled;

[0021] Fig. 5 is a cross-sectional view of an alternative embodiment of an injector according to the present disclosure, with a container needle in a storage state wherein the needle partially penetrates a unitary wall of the container;

[0022] Fig. 6 is a cross-sectional view of a further alternative embodiment of an injector according to the present disclosure, with a container needle in a storage state wherein the needle partially penetrates a unitary wall of the container;

[0023] Fig. 7 is a cross-sectional view of an embodiment of an injector according to the present disclosure, with a container needle in a storage state wherein the needle partially penetrates a barrier, but not a flexible wall, of a seal assembly;

[0024] Fig. 8 is a cross-sectional view of an alternative embodiment of an injector according to the present disclosure, with a container needle in a storage state wherein the needle partially penetrates a barrier, but not a flexible wall, of a seal assembly;

[0025] Fig. 9 is a cross-sectional view of a variant to the embodiment of Fig. 8 including vents to evacuate a space between a flexible wall and an exteriorly disposed barrier as an associated container needle is moved between a storage state and a delivery state;

[0026] Fig 10 is a cross-sectional view of an additional variant to the embodiment of Fig. 8 including bypasses to evacuate a space between a flexible wall and an exteriorly disposed barrier as an associated container needle is moved between a storage state and a delivery state;

[0027] Fig 11 is a cross-sectional view of the container of Fig. 10 in an intermediate state with the bypasses in fluid communication with a space defined between a flexible wall and a barrier;

[0028] Fig. 12 is a cross-sectional view of an injector according to a still further embodiment of the present disclosure where a sterile condition is maintained in a reservoir until actuation of the fluid delivery system;

[0029] Fig. 13 is a cross-sectional view of a variant of the injector illustrated in Fig. 12;

[0030] Fig. 14 is a cross-sectional view of a further variant of the injector illustrated in Fig. 12; and

[0031] Fig. 15 is a flowchart illustrating a method of assembling an injector according to the present disclosure.

Detailed Description of Various Embodiments

[0032] Although the following text sets forth a detailed description of different embodiments of the invention, it should be understood that the legal scope of the invention is defined by the words of the claims set forth at the end of this patent. It should also be understood that, unless a term is expressly defined in this patent using the sentence "As used herein, the term '_____' is hereby defined to mean..." or a similar sentence, there is no intent to limit the meaning of that term, either expressly or by implication, beyond its plain or ordinary meaning, and such term should not be interpreted to be limited in scope based on any statement made in any section of this

patent (other than the language of the claims). To the extent that any term recited in the claims at the end of this patent is referred to in this patent in a manner consistent with a single meaning, that is done for sake of clarity only so as to not confuse the reader, and it is not intended that such claim term be limited, by implication or otherwise, to that single meaning. Finally, unless a claim element is defined by reciting the word "means" and a function without the recital of any structure, it is not intended that the scope of any claim element be interpreted based on the application of 35 U.S.C. §112, sixth paragraph.

[0033] The detailed description is to be construed as exemplary only and does not describe every possible embodiment of the invention because describing every possible embodiment would be impractical, if not impossible. Numerous alternative embodiments could be implemented, using either current technology or technology developed after the filing date of this patent, which would still fall within the scope of the claims defining the invention. Along these lines then, several embodiments according to the present disclosure are illustrated in Figs. 1-3 and 5-14.

[0034] In general terms, an injector according to the present disclosure includes a container, a fluid delivery system and an actuator. While reference is made to an injector, which in some instances may refer to a delivery device that ensures that a set volume of drug product is delivered, it will be understood that this disclosure also encompasses infusion devices, which in some instances may refer to a delivery device that ensures that a particular rate of delivery is achieved. It should also be understood that the terms injector and infuser may be used interchangeably when referring to embodiments in the specification.

[0035] As illustrated in Figs. 1-3 and 5-11, the container may include a wall with an interior surface and a seal assembly with an interior surface, the interior surfaces of the wall and the seal assembly defining a closed sterile reservoir filled with a drug product. Moreover, the fluid delivery system illustrated in these embodiments may include a sterile container needle, which may also be unsheathed, having a point disposed only partially through the seal assembly in a storage state, and disposed through the interior surface of the seal assembly into the sterile reservoir in a delivery state. As such, the needle is in fluid communication with the container in the delivery state, but not the storage state. According to these embodiments, the injector may include an actuator that is adapted to move the container needle from the storage state

to the delivery state, which may involve movement of the needle relative to the container or of the container relative to the needle, as is discussed in greater detail below.

[0036] As is illustrated in Figs. 1, 3, and 4-6, the seal assembly may be a flexible unitary wall having an interior surface that defines the interior surface of the seal assembly, and the point of the container needle may be disposed partially into the unitary wall. Alternatively, as illustrated in Figs. 7-11, the seal assembly may include a flexible wall with an interior surface that defines the interior surface of the seal assembly, and a barrier disposed exterior of the flexible wall to define an enclosed space between the flexible wall and the barrier. According to such embodiments, the point of the container needle is disposed through the barrier into the space in the storage state.

[0037] Still further alternatives will be discussed in the context of each of the embodiments illustrated herein.

[0038] Referring then to Fig. 1, an injector 100 is illustrated therein. The injector 100 includes a container 102, a fluid delivery system 104, and an actuator 106.

[0039] The container 102 (which also may be referred to as a cartridge herein) includes a wall 110 with an interior surface 112 and an exterior surface 114. While a unitary (i.e., one-piece) wall 110 has been illustrated in Fig. 1 that defines both the interior and exterior surfaces 112, 114, it will be understood that according to other embodiments the wall 110 may include a plurality of layers with different layers defining the interior and exterior surfaces 112, 114.

[0040] According to certain embodiments of the present disclosure, the wall 110 is rigid. According to other embodiments, the wall 110 may be flexible, whether according to the nature of the material that defines the wall or according to the nature of the structure of wall (e.g., a bellows construction). The wall 110 may be made of glass, metal, or polymer, for example. In particular, polymer versions may be made of polycarbonate, polypropylene, polyethylene (such as high density polyethylene), polytetrafluoroethylene, cyclic olefin polymer, cyclic olefin copolymer, Crystal Zenith olefinic polymer (available from Daikyo Seiko, Ltd., Japan), nylon, or engineering resins, for example. As to flexible versions of the wall 110, butyl rubber, silicon-based rubber, latex-based rubber, coated rubber, as well as multi-layer

polymer films, such as may include polyethylene (such as low density polyethylene) and polypropylene, may be used.

[0041] The wall 110 may have a generally cylindrical shape, which a shoulder 120 separating a first cylindrical section 122 having a first cross-sectional diameter from a second cylindrical section 124 having a second cross-sectional diameter, the first cross-sectional diameter being smaller than the second cross-sectional diameter. The wall 110 may also define two opposed, open ends 126, 128. The wall 110, or more particularly the interior surface 112 of the wall 110, may also define a bore 130.

[0042] The container 102 may include a flexible unitary wall 140 (which may also be referred to as a seal or septum) having an interior surface 142 and an exterior surface 144. The wall 140 may be disposed in the first open end 126 defined by the wall 110 and fixedly attached to the wall 110 of the container 102 such that there is limited relative movement between the wall 140 and the wall 110, for example at the points of attachment of the wall 140 to the wall 110 across the open end or opening 126. Moreover, the interior surfaces 112, 142 of the wall 110 and the flexible wall 140 may define, at least in part, a closed sterile reservoir 150 that is filled with a drug product 160, described in greater detail below. The wall 140 may be made of bromobutyl, chlorobutyl, or chlorobromobutyl rubber, fluoropolymer rubber, natural rubber, silicon-based rubber, silicon, or santoprene, for example.

[0043] The container 102 may also include a stopper or piston 170 with interior and exterior surfaces 172, 174. The piston 170 may be received within the end 128 defined by the wall 110, and may be moveable along the bore 130 between the ends 126, 128 of the container 102. According to such an embodiment, the reservoir 150 within which the drug product 160 is disposed may be defined by the interior surfaces 112, 142, 172 of the walls 110, 140 and piston 170.

[0044] The container 102 may be used in conjunction with the fluid delivery system 104, the relevant portions of which are illustrated in Fig. 1. In particular, the fluid delivery system 104 may include a container needle 180 having a point 182. As illustrated, the point 182 is disposed only partially into the flexible wall 140 in a storage state. The penetration of the point 182 of the needle 180 into the wall 140 may be controlled through a number of methods and/or mechanisms. For example, Fig. 2 illustrates a jig that may be used in combination with the container 102 to control the depth to which the point 182 penetrates the wall 140.

[0045] The fluid delivery system 104 may also include an injection needle 190 with a point 192. The point 192 of the injection needle 190 may be covered with a needle shield 194 to prevent contact with and contamination of the point 192. The container needle 180 and the injection needle 190 may be connected by a cannula or tube 200, which may be a flexible cannula according to certain embodiments of the present disclosure. The needle 190, like the needle 180, may be made of stainless steel, for example. According to other embodiments, the container needle 180 and the injection needle 190 may be formed integrally (i.e., as one piece).

[0046] Fluid delivery system 104 may be used in conjunction with the actuator 106, mentioned previously and illustrated schematically in Fig. 1. The actuator 106 may be adapted to move at least the container needle 180 between the storage state illustrated in Fig. 1 and a delivery state illustrated in Fig. 3, and thus to move the fluid delivery system 104 between the storage and delivery states. In the delivery state, the container needle 180 is disposed through the interior surface 142 of the flexible wall 140 into the sterile reservoir 150 and is in fluid communication with the reservoir 150.

[0047] The movement of the needle 180 between the states may occur in a variety of fashions. For example, the needle 180 may be held fixed relative to the housing of the injector 100, and the container 102 may move relative to the needle 180 and the housing. Alternatively, the container 102 may be held fixed relative to the housing, and the needle 180 may be moved relative to the container 102 and the housing. It may also be possible for both container 102 and needle 180 to move relative to the housing of the injector 100. It will be understood that all of these actions may be embraced within the statement that the actuator 106 is adapted to move the container needle 180 between the storage and delivery states.

[0048] The actuator 106 may be mechanical, electro-mechanical, or electrical. For example, the actuator 106 may include a solenoid, motor-driven lever, motor with associated gearing, etc. It may even be possible to provide a tab or button attached to the container 102 or the needle 180 to permit the user to achieve the relative motion between the container 102 and the needle 180 manually. In fact, the container 102 may be received within a tab or button that is depressed into the housing when the injector 100 is activated to move the container 102 relative to the (fixed) needle 180.

[0049] The actuator 106 may move the container needle 180 between storage and delivery states by moving the needle 180 from the storage state to the delivery state,

or by moving the needle 180 from the delivery state to the storage state. In fact, the actuator may move the container needle 180 between the storage and delivery states repeatedly (i.e., multiple times or repetitions). Furthermore, the actuator 106 may move the container needle 180 immediately upon receipt of an input or signal (e.g., as generated through the depression or manipulation of a button, switch or other input device, which may be mechanical, electro-mechanical or electrical in nature, coupled to the actuator 106), or may delay movement of the container needle 180 between storage and delivery states some period of time after an input is received. According to a particular embodiment, the actuator 106 may delay movement of the needle 180 from the storage state to the delivery state until after such a time delay.

[0050] As mentioned previously, both the reservoir 150 and the container needle 180 are described as sterile, while the remainder of the delivery device is described as clean. These terms describe the condition of the reservoir 150, the needle 180 or remainder of the delivery device as a consequence of their assembly under conditions that will ensure a specified level of freedom from contamination, wherein a sterile object or device is understood to have a relatively higher level of freedom from contamination than a clean object or device. By way of non-limiting example, the concepts of sterility and cleanliness may be discussed with reference to the schematic of Fig. 4, which discussion will be recognized applies not only to the embodiment illustrated in Figs. 1 and 3, but all of the embodiments described herein.

[0051] Fig. 4 illustrates a manufacturing facility 250, and may be used to discuss a manufacturing process that is conducted within the facility 250. It will be noted that the facility 250 is divided into a plurality of spaces 252, 254, 256, 258, 260, 262, 264, 266, 268, which divisions may be maintained through the use of permanent or semi-permanent walls or other barriers. As will be understood, certain spaces or regions may be divided without barriers or walls, but may simply be separated on an organizational level instead. Additionally, it will be recognized that a greater or lesser number of spaces or an alternative arrangement of the spaces may be used, such differing numbers or arrangements of spaces being readily determinable by one of ordinary skill in the art.

[0052] The components of the container 102 (walls 110, 140, and stopper/piston 170) and the fluid delivery system 104 would enter the facility 250 through space 252, wherein the components are sterilized using e-beam technology, for example. In the

alternative, while the container 102 and the fluid delivery system 104 are defined as separate structures with reference to the embodiments of Figs. 1 and 3, it would also be known to use the manufacturing process described herein with a product where the container 102 is attached to the fluid delivery system 104 prior to introduction into the space 254 (e.g., the container 102/fluid delivery system 104 is a syringe), and to sterilize the product. Also in the alternative, the components may be sterilized through other currently-known (e.g., treatment with chlorine dioxide or vapor phase hydrogen peroxide) or later-developed sterilization procedures as the components enter the facility 250 at entry points 252, 264, 266. The container 102 and fluid delivery system 104 would then pass into space 254 for filing with the drug product. The space 254 may be operated as an aseptic Class 100 clean room. A Class 100 clean room is one in which the number of particles of size 0.5 μm or larger permitted per cubic foot of air is less than 100. Once the fill has been performed and the stopper 170 has been disposed in the end 128 of the container 102, the container needle 180 is inserted partially into wall/septum 140. Because the container needle 180 does not penetrate through the wall 140, the reservoir 150 and the drug product 160 remains sterile (i.e., at the higher level of cleanliness). Moreover, because the fluid delivery system 104 is sterile and is assembled to the container 102 under sterile conditions, the fluid delivery system 104 is believed to remain sterile, in part because of the partial insertion of the container needle 180 and in part because of the shield 194.

[0053] The prefilled containers 102 in combination with the associated fluid delivery systems 104 (which combination may be referred to as a prefilled, sterile container combination, or in those embodiments wherein the fluid delivery system 104 and containers 102 are attached or formed integrally with each other (e.g., a syringe), the container 102 and the fluid delivery system 104 may also be referred to as prefilled sterile syringes) are then moved through transfer space 256 (also operated as a Class 100 clean room, wherein certain embodiments are also aseptic) before being received within storage space 258. The prefilled, sterile container combinations are moved from the storage space 258 into inspection area 260 (aseptic in certain embodiments), wherein the prefilled, sterile container combinations are inspected prior to assembly with the actuator 106 and other elements of the injector 100. Because the drug product 160 is contained within the sealed container 102 and the sterility of the fluid delivery system 104 is preserved at this point (i.e., the container

needle 180 is inserted into the wall 140 and the injector needle 190 is capped with the shield 194), the inspection area may be operated as a Class 10,000 clean room. Once inspected, the prefilled, sterile container combinations may be passed from inspection space 260 to assembly space 262.

[0054] Similar to the inspection space 260, the assembly space 262 may be operated as an aseptic Class 10,000 clean room, or even a Class 100,000 clean room. Materials being passed into the clean room from spaces 264, 266 may be in a sterile condition, or may be sterilized using e-beam technology, for example. Within the assembly space 262, the remainder of the injector 100 (e.g., the actuator 106) may be assembled (i.e., the container 102 and the fluid delivery system 104 may be disposed in the remainder of the injector 100) prior to the injector 100 passing into the packaging space 268.

[0055] Other processing, in addition to assembly, may occur at this point. According to certain embodiments, it may desirable to arrange the fluid delivery system 104 in one configuration prior to assembly with the remainder of the injector 100, for ease of transport for example, but to have the fluid delivery system 104 assume a different arrangement once assembled in the injector 100. For example, it may be desirable for the fluid path between the container needle 180 and the injector needle 190 to have straight configuration prior to assembly with the remainder of the injector, but to assume a curved, bent (e.g., 60 degrees, 90 degrees, etc) or other non-straight configuration when assembled with the remainder of the injector 100. By maintaining the fluid delivery system 104 in a straight configuration, the spacing between the prefilled, sterile container combinations in a tray or other holder used to transport the prefilled, sterile container combinations may be maximized in that the additional room required to accommodate a curved, bent or other non-straight configuration may be avoided. This may also have an effect on the costs of filling the containers 102, in that each tray can accommodate a larger number of container 102/fluid delivery system 104 combinations, and thus the number of trays passing through the space 254 may be limited. The change in configuration may be performed in the assembly space 262, for example, so as to minimize the need to accommodate the curved, bent or otherwise non-straight fluid delivery systems 104 elsewhere in the facility 250.

[0056] It will be recognized that the embodiment of the injector 100 illustrated in Figs. 1 and 3 is simply an exemplary embodiment according to the present disclosure. To this end, Figs. 5 and 6 illustrate variants of the injector illustrated in Figs. 1 and 3.

[0057] According to the embodiment of Fig. 5, the injector 300 includes a container 302, a fluid delivery device 304 and an actuator 306. Similar to the embodiment of Figs. 1 and 3, the container 302 includes a wall 310 with interior and exterior surfaces 312, 314. Moreover, the wall 310 may have two opposed ends 320, 322 with the interior surface 312 of the wall 310 defining a bore 324 between the opposing ends 320, 322.

[0058] However, unlike the container 102, the container 302 has a fixed plug 326 that closes the end 320. In addition, while the container 302 has a flexible unitary wall 330 with interior and exterior surfaces 332, 334, the wall 330 is disposed within the end 322 of the container 302, and thus performs the role of the stopper/piston 170 in the container 102. Consequently, the wall 330 is moveable along the bore 324 between the opposing ends 320, 322. Moreover the interior surfaces 312, 332 of the walls 310, 330 define a sterile reservoir 340 in which a drug product 350 is disposed.

[0059] According to this embodiment, the fluid delivery device 304 may include a sterile container needle 360 having a point 362. The point 362 of the needle 360, like the point 182 of the needle 180, is disposed only partially into the flexible wall 330 in a storage state, with the actuator 306 causing the point 362 to move between the storage state and a delivery state wherein the point 362 is disposed through the interior surface 332 of the flexible wall 330 into the sterile reservoir 340. The container needle 360 may be in fluid communication with a injection needle 370 having a point 372 covered with a shield 374 through a cannula 380 received within a piston rod 382, for example, which rod 382 may be used to move the stopper/piston 330 between the ends 320, 322 of the container 302.

[0060] Fig. 6 shows a closely related variant to that illustrated in Fig. 5. According to the variant illustrated in Fig. 6, a container has a wall 390 with interior and exterior surfaces 392, 394. However, unlike the containers discussed previously, the wall 390 defines a closed end 396 and an open end 398. The container also includes a flexible wall 400, like the wall 330 of the embodiment of Fig 5, which wall 400 is moveable within the container between the open end 398 and the closed end 396. According to this embodiment, a separate structure is not required to close off

one of the ends 396, 398 because the wall 390 already defines the closed end 396 itself. For that matter, the closed end 396 may be resized so that it is radially larger than illustrated in Fig. 6.

[0061] Having thus discussed a plurality of embodiments wherein a seal assembly includes only a flexible unitary wall, a further plurality of embodiments will be discussed with reference to Figs. 7-11 wherein the seal assembly includes a plurality of walls and/or seals. This structure may also be referred to as a compartmentalized seal (or septum with reference to Fig. 7, or stopper with reference to Figs. 8-11).

[0062] Referring first to Fig. 7, an injector 450 includes a container 452, a fluid delivery system 454, and an actuator 456.

[0063] The container 452 includes a wall 460 with an interior surface 462 and an exterior surface 464. Like the container of Figs. 1 and 2, the wall 460 may have a generally cylindrical shape, with a shoulder 470 separating a first cylindrical section 472 having a first cross-sectional diameter from a second cylindrical section 474 having a second cross-sectional diameter, the first cross-sectional diameter being smaller than the second cross-sectional diameter. The wall 460 may also define two opposed, open ends 476, 478. The wall 460, or more particularly the interior surface 462 of the wall 460, may also define a bore 480.

[0064] Unlike the container 102 of Figs. 1 and 3, the container 452 of Fig. 7 has a seal assembly that includes more than a single, unitary wall. The seal assembly of the container 452 includes a flexible wall 490 and a barrier 492. The flexible wall 490 has an interior surface 494 and an exterior surface 496, while the barrier 492 has an interior surface 498 and an exterior surface 500. The interior surfaces 462, 494 of the wall 460 and the flexible wall 490 defining a closed sterile reservoir 510 filled with a drug product 520. On the other hand, the barrier 492 is disposed exterior of the flexible wall 490 to define an enclosed space 530 between the flexible wall 490 and the barrier 492. The space 530 may be defined by the interior surface 462 of the wall 460, the exterior surface 496 of the flexible wall 490, and the interior surface 498 of the barrier 492.

[0065] As illustrates, the container 452 may also include a stopper or piston 540 with interior and exterior surfaces 542, 544. The piston 540 may be received within the end 478 defined by the wall 460, and may be moveable along the bore 480

between the ends 476, 478 of the container 452. According to such an embodiment, the reservoir 510 within which the drug product 520 is disposed may be defined by the interior surfaces 462, 494, 542 of the walls 460, 490 and piston 540.

[0066] The embodiment of Fig. 7 also includes the fluid delivery system 454 comprising a sterile container needle 550 having a point 552 disposed through the barrier 492 into the space 530 in a storage state, and disposed through the interior surface 494 of the flexible wall 490 into the sterile reservoir 510 in a delivery state. In this sense, the container needle 550 only partially penetrates the seal assembly. The fluid delivery system 454 may also include an injection needle 560 with a point 562 covered at least initially with a needle shield 564 to prevent contact with and contamination of the point 562. The container needle 550 and the injection needle 560 may be connected by a cannula or tube 570, which may be a flexible cannula according to certain embodiments of the present disclosure.

[0067] As was the case with the embodiment of Figs. 1 and 3, the present disclosure includes a number of variants for the embodiment illustrated in Fig. 7, which variants are illustrated in Figs. 8-11.

[0068] The embodiment of Fig. 8 is similar to the embodiment of Fig. 7 in the way that the embodiment of Fig. 5 was similar to that of Figs. 1 and 3. In particular, the seal assembly of an injector 600 according to the embodiment of Fig. 8 is disposed in a container 602 in place of the stopper/piston 540 illustrated relative to the container 452. That is, the container 602 includes a wall 604 that defines a bore 606, and a flexible wall 608 and a barrier 610 each define a stopper that is moveable along the bore 606. While the wall 604 of the container 602 does not define opposing open and closed ends in the embodiment illustrated, such an alternative is possible according to the present disclosure similar to Fig. 6.

[0069] Figs. 9-11 illustrate variants to the embodiment illustrated in Fig. 8, which variants include additional features to permit the space or region between the flexible wall and the barrier to be evacuated or exhausted. These additional features may be referred to as vents, valves or bypasses, but all of these structures permit gases to escape from the space or region between the flexible wall and the barrier when an actuator moves the associated container needle from a storage state to a delivery state. This is not to suggest that the inner wall and exterior barrier cannot remain separated, for example through the use of a spacer or spacers, according to other embodiments of

the present disclosure. However, the alternatives of Figs. 9-11 illustrate options for evacuating the space as to those embodiments where the inner wall and exterior barrier come together. It would be understood, however, that the vents, valves, and bypasses would preserve a sterile condition within the space until the space is evacuated or exhausted.

[0070] A container 650 is illustrated in Fig. 9 including a wall 652 and a seal assembly, the assembly including a flexible wall 654 and a barrier 656. The flexible wall 654 has an interior surface 658 and an exterior surface 660, while the barrier 654 has an interior surface 662 and an exterior surface 664. An interior surface 668 of the wall 652 and the interior surface 658 of the flexible wall 654 defining a closed sterile reservoir 670 filled with a drug product 680. The barrier 656 is disposed exterior of the flexible wall 654 to define an enclosed space 690 between the flexible wall 654 and the barrier 656. The space 690 may be defined by the interior surface 668 of the wall 652, the exterior surface 660 of the flexible wall 652, and the interior surface 662 of the barrier 656.

[0071] As is also illustrated in Fig. 10, a fluid delivery system 700 including a container needle 702 is used in conjunction with the seal assembly. The container needle 702 is illustrated in the storage state, wherein the container needle 702 is disposed through the barrier 656 so that a point 704 of the needle 702 is disposed in the space 690. The point 704 will penetrate the flexible wall 654 and depend into the reservoir 670 in a delivery state, not shown. It will be recognized that the needle 702 is not drawn to scale particularly as to its length, as is true of other embodiments illustrated here.

[0072] In contrast with the previously discussed embodiments, the container 650 illustrated in Fig. 9 includes at least one vent 710. The vents 710 are in fluid communication with the space 690 between the barrier 656 and the flexible wall 654. The vents 710 are selectively actuated to permit gas trapped between the barrier 656 and the flexible wall 654 to escape through the vents 710 when the seal assembly is moved between the illustrated storage state and the delivery state, wherein the barrier 656 is advanced in the direction of the flexible wall 654 to permit the point 704 of the container needle 702 to penetrate through the wall 654. However, the vents 710 may be in a sealed condition relative to the environment until actuated, for example, by a change in the pressure within the space 690.

[0073] As illustrated, the vents 710 are disposed within the barrier 656, and extend between the interior surface 662 and the exterior surface 664 of the barrier 656. A flap 712 covers the end of the vent 710 proximate to the exterior surface 664, and thereby seals the end of the vent 710 until the vent is actuated, preserving the sterility of the space 690 between the barrier 656 and the flexible wall 654. Alternatively, the vents 710 may be arranged, for example, in the wall 652 of the container 650.

[0074] Figs. 10 and 11 illustrate a further variant on the system of Fig. 8, wherein a container 720 includes a wall 722 and a seal assembly, the assembly including a flexible wall 724 and a barrier 726. The flexible wall 724 has an interior surface 728 and an exterior surface 730, while the barrier 726 has an interior surface 732 and an exterior surface 734. An interior surface 738 of the wall 722 and the interior surface 728 of the flexible wall 724 define a closed sterile reservoir 740 filled with a drug product 750. The barrier 726 is disposed exterior of the flexible wall 724 to define an enclosed space 760 between the flexible wall 724 and the barrier 726. The space 760 may be defined by the interior surface 738 of the wall 722, the exterior surface 730 of the flexible wall 722, and the interior surface 732 of the barrier 726.

[0075] As is also illustrated in Fig. 10, a fluid delivery system 770 including a container needle 772 is used in conjunction with the seal assembly. The container needle 772 is illustrated in the storage state, wherein the container needle 772 is disposed through the barrier 726 so that a point 774 of the needle 772 is disposed in the space 760. The point 774 will penetrate the flexible wall 724 and depend into the reservoir 740 in a delivery state, not shown.

[0076] In contrast with the previously discussed embodiments, the container 720 illustrated in Fig. 10 includes at least one bypass or vent 780. The bypasses 780 are in fluid communication with the reservoir 740. The bypasses 780 are selectively actuated to permit gas trapped between the barrier 726 and the flexible wall 724 to escape through the bypasses 780 into the reservoir 740 when the seal assembly is moved between the illustrated storage state and the delivery state, wherein the barrier 726 is advanced in the direction of the flexible wall 724 to permit the point 774 of the container needle 772 to penetrate through the wall 724.

[0077] However, the bypasses 780 are not in fluid communication with the space 760 until the flexible wall 724 has moved from the storage state illustrated in Fig. 10

to an intermediate state illustrated in Fig. 11. As illustrated in Figs. 10 and 11, the bypasses 780 may be defined in the interior surface 738 of the wall 722, and as illustrated may take the form of a groove 782 formed in the wall 722. The groove 782 may have a distal end 784 and a proximal end 786. As will be recognized, until the exterior surface 730 of the flexible wall 724 moves past the distal end 784 of the grooves 782, the reservoir 740 is in a sealed condition relative to the space 760. However, once the exterior surface 730 of the flexible wall 724 moves past distal end 784 of the grooves 782, the gases trapped between the barrier 726 and the flexible wall 724 may exhaust into the reservoir 740. This may facilitate the movement of the barrier 726 and needle 770 toward the flexible wall 724.

[0078] While all of the forgoing embodiments have focused to one degree or another on a fluid delivery system partially disposed through a seal assembly, there are other alternatives where the container needle is not disposed through the seal assembly, or where the container needle is disposed fully through the seal assembly. Two such alternatives are illustrated in Figs. 12 and 13.

[0079] Figs. 12 and 13 illustrate embodiments wherein the container needle is disposed through the flexible wall (defining the stopper or septum) and a valve is used to seal the reservoir off from the injection needle. The valve may also be used to control the flow of drug product from the reservoir in the container. In this fashion, the valve may be used to meter an amount of drug product from the reservoir, or to delay the flow of the drug product until a time delay has elapsed relative to receipt of an input from an input device (e.g., button or switch), for example.

[0080] As such, Fig. 12 illustrates an injector 850 with a container 852, a fluid delivery system 854 and an actuator 856. The container 852 includes at least a flexible wall 860, which may be in the form of a septum according to the illustrated embodiment. The flexible wall 860 has an interior surface 862 and an exterior surface 864. Additionally, the fluid delivery system 854 includes a container needle 866, an injection needle 868, and a flexible cannula or tubing 870 connecting the container needle 866 and the injection needle 868. The injection needle 868 may be received within a cover 872 that preserves the sterility of the needle 868.

[0081] On the other hand, the container needle 866 (and in particular a point 874 of the container needle 866) is disposed through the flexible wall 860 through the interior surface 862. The needle 866 is thus in fluid communication with a sterile

reservoir 880 and a drug product 890 disposed within the reservoir 880. Fluid communication between the container needle 866 and the injection needle 868 is interrupted by a valve 900 disposed in or along the flexible tubing 870. Thus, unlike the other embodiments discussed above relative to Figs. 1-11, the actuator 856 of the injector 850 is not used to move the container needle 866 relative to the flexible wall 860, but instead to manipulate the valve between a closed state wherein fluid communication is interrupted between the needles 866, 868 and an open state wherein the container needle 866 is in fluid communication with the injection needle 868.

[0082] It will be recognized that the valve 900 may take a variety of shapes and forms, two of which are illustrated in Figs. 12 and 13. In particular, Fig. 12 illustrates an embodiment of the injector 850 wherein a rotatable valve 900 is disposed in the flexible tubing 870, or has an internal valve member that is in fluid communication with the fluid flow path defined between the container needle 866 and the injection needle 868. Fig. 13, by contrast, illustrates and embodiment of the injector wherein a pinch valve 902 is disposed along the flexible tubing 870, and thus cooperates with an exterior surface of the tubing 870 to interrupt the fluid communication between the container needle 866 and the injection needle 868.

[0083] Embodiments such as are illustrated in Figs. 12 and 13 would also work well with a container that has a permanently attached needle, such that the container is in the form of a syringe, for example. For that matter, the method described relative to Fig. 4 would work well with any of the embodiments mentioned heretofore, as well as with an embodiment like that illustrated in Figs. 12 and 13 wherein no valve is used, but the syringe (i.e., a container with permanently attached needle) has an injection needle that is covered by a shield to maintain its sterility, as mentioned above.

[0084] It will be further understood that the embodiments illustrated in Figs. 12 and 13 may be further modified to incorporate a seal assembly including a plurality of walls and/or seals, such as is illustrated in Fig. 7, for example. Fig. 14 illustrates such an embodiment.

[0085] In particular, Fig. 14 illustrates an injector 920 with a container 922, a fluid delivery system 924, an actuator 926, and a seal assembly 928. The fluid delivery system 924 may include a container needle 930, an injection needle 932, and a flexible cannula or tubing 934 connecting the container needle 930 and the injection

needle 932. The injection needle 932 may be received within a cover 936 that preserves the sterility of the needle 932. The needle 932 may also be in selective fluid communication with a sterile reservoir 940 and a drug product 942 disposed within the reservoir 940 via a valve 944 disposed in or along the flexible tubing 934. In this regard, the injector 920 is similar to those illustrated in Figs. 12 and 13.

[0086] However, the seal assembly 928 of the injector 920 also has a flexible wall 950 and a barrier 952. The flexible wall 950 and the barrier 952 each have interior and exterior surfaces, with the interior surface of the flexible wall 950 defining, in part, the closed sterile reservoir 940. On the other hand, the barrier 952 is disposed exterior of the flexible wall 950 to define an enclosed space 954 between the flexible wall 950 and the barrier 952 in which a point 956 of the container needle 930 may be disposed.

[0087] In this regard, the embodiment of Fig. 14 has two potential barriers: one in the form of the valve 944 and a second in the form of the placement of the point 956 within the space 954. In fact, the valve 944 may be controlled to provide a delay in the injection of the drug product 942 after the container needle 930 has been caused to penetrate trough the flexible wall 950 into the reservoir 940.

[0088] As will be recognized, the devices according to the present disclosure may have one or more advantages relative to conventional technology, any one or more of which may be present in a particular embodiment in accordance with the features of the present disclosure included in that embodiment. As one example, these embodiments maintain the sterility of the drug product until the time of use. As another example, the potential for mixing of the drug product is limited or eliminated prior to the time of use. As a still further example, unintended delivery of the drug product is limited or prevented prior to the time of use.

[0089] For illustrative purposes only, Fig. 15 provides a further method 1000 for assembling delivery devices according to any of the embodiments disclosed above. The method 1000 follows the general processing flow outlined above relative to Fig. 4. However, rather than referring to the cleanroom classifications according to U.S. Federal Standard 209E, reference is made to cleanroom classifications according to the GMP EU standard. Moreover, the method 1000 provides additional optional paths (represented as a left or right branch) that may be followed in the assembly of

the delivery device. Consequently, the method 1000 of Fig. 15 may be viewed as supplementary to the discussion above relative to Fig. 4.

[0090] The method 1000 for assembling delivery devices begins at block 1002. The containers used in the device are initially stored in sealed tubs. As mentioned above, these containers may be or may have been sterilized at some point. At block 1002, the tubs are debagged, for example using an automated debagger in a Grade C cleanroom. At block 1004, the Tyvek seal is peeled off (e.g., by a robot) and removed, for example, in a space operated as a Grade A cleanroom, perhaps within an isolator in a space otherwise operated a Grade C cleanroom.

[0091] The containers are filled, and the stoppers and the fluid systems are attached, and then the containers are re-nested in open tubs, at block 1006, in a space operated as a Grade A cleanroom, perhaps within an isolator in a space otherwise operated a Grade C cleanroom. From this point, two different alternative paths, or branches, are possible.

[0092] The filled containers may be left in the open tubs at block 1008. The tubs may be conveyed and carted to a storage space (e.g., cold room) at block 1010.

[0093] If the route of block 1008, 1010 is followed, then the method 1000 may continue with the tubs being transferred for processing to an inspection room at block 1012. The filled containers are then denested from the open tubs at block 1014, and supplied to an automated inspection machine at block 1016. Automated inspection of the filled containers occurs at block 1016, followed by optional, additional semi-automated or manual inspection at block 1018.

[0094] Alternatively, the tubs may be resealed, rebagged, and labeled, at block 1020. For example, the tubs may be resealed with Tyvek (e.g., using a Bausch + Strobel tub sealer), rebagged, and then labeled in a Grade C cleanroom at block 1020. The tubs may then be stored, or even shipped, if necessary, at blocks 1022, 1024.

[0095] Once storage or transport is completed, the tubs are debagged, for example using an automated debagger at block 1026. At block 1028, the Tyvek seal is peeled off and removed. The filled containers may then be denested for inspection, at block 1030. The actions at blocks 1026, 1028, 1030 are performed in a Grade C cleanroom. An automated inspection may then be carried out using a visual inspection machine designed for operation in a Grade C cleanroom at block 1032.

[0096] Following either procedure, the filled, inspected containers may then be transferred to rondo trays at block 1034.

[0097] According to a first procedure, the rondo trays may be sent directly to storage at block 1036. If the route of block 1036 is followed, then the rondo trays are transferred for processing to the device assembly room at block 1038. The containers are denested at block 1040, and assembled with the other elements of the delivery device at block 1042 to define an assembled delivery device (e.g., an injector or an infuser).

[0098] Alternatively, the containers may be moved into tubs, which are sealed, bagged, and labeled, at block 1044. For example, the tubs may be resealed with Tyvek, bagged, and then labeled in a Grade C cleanroom. The tubs may then be stored, or even shipped for further processing, if necessary, at blocks 1046, 1048. Once storage or transport completed, the tubs are debagged, for example using an automated debagger at block 1050. At block 1052, the Tyvek seal is peeled off and removed, and the containers are denested. The filled containers may then be assembled with the other elements of the delivery device at block 1054. The actions at blocks 1050, 1052, 1054 may all occur in a Grade C cleanroom.

[0099] In either event, the assembled devices are packaged at block 1056, and the packaged, assembled devices are stored at block 1058. Finally, the packaged, assembled devices are transported to the distributor, and/or for other distribution actions at block 1060.

[00100] Other advantages not specifically listed herein may also be recognized as well. Moreover, still other variants and alternatives are possible.

[00101] As an example, while the operation of the actuator has been described in regard to the foregoing embodiments as moving, for example, the container needle from a storage state to a delivery state, it will be understood that the actuator may also move the container needle from the delivery state to the storage state. For example, if a dose of drug product is to be delivered that is less than the volume of the reservoir (such as may be the case wherein the injector is designed to be programmed to deliver an adjustable dose according to the needs of the patient (e.g., pediatric vs. adult patient)), then the actuator may move the container needle from the storage state to the delivery state prior to delivery of the dose, and from the delivery state to the storage state after delivery of the dose. The movement from the delivery state to the

storage state will in effect reseal the container and close the fluid path to the patient. This sequence of movement between the storage state and the delivery state may be repeated. As noted above, maintaining a closed fluid path until delivery is initiated is advantageous in that the opportunity for unintended delivery of the drug product to the patient and/or mixing of the drug product with the patient's bodily fluids is reduced.

[00102] The injectors according to the present disclosure may be used with a variety of drug products, including colony stimulating factors, such as granulocyte colony-stimulating factor (G-CSF), may be administered to increase the number of immune cells (e.g., white blood cells) found in bone marrow or peripheral blood. Such G-CSF agents include, but are not limited to, Neupogen® (filgrastim) and Neulasta® (pegfilgrastim).

[00103] In other embodiments, the injector may be used with various other products including, for example, an erythropoiesis stimulating agent (ESA), which may be in a liquid or a lyophilized form. An ESA is any molecule that stimulates erythropoiesis, such as Epogen® (epoetin alfa), Aranesp® (darbepoetin alfa), Dynepo® (epoetin delta), Mircera® (methyoxy polyethylene glycol-epoetin beta), Hematide®, MRK-2578, INS-22, Retacrit® (epoetin zeta), Neorecormon® (epoetin beta), Silapo® (epoetin zeta), Binocrit® (epoetin alfa), epoetin alfa Hexal, Abseamed® (epoetin alfa), Ratioepo® (epoetin theta), Eporatio® (epoetin theta), Biopoin® (epoetin theta), epoetin alfa, epoetin beta, epoetin zeta, epoetin theta, and epoetin delta, as well as the molecules or variants or analogs thereof as disclosed in the following patents or patent applications, each of which is herein incorporated by reference in its entirety: U.S. Pat. Nos. 4,703,008; 5,441,868; 5,547,933; 5,618,698; 5,621,080; 5,756,349; 5,767,078; 5,773,569; 5,955,422; 5,986,047; 6,583,272; 7,084,245; and 7,271,689; and PCT Publ. Nos. WO 91/05867; WO 95/05465; WO 96/40772; WO 00/24893; WO 01/81405; and WO 2007/136752.

[00104] An ESA can be an erythropoiesis stimulating protein. As used herein, "erythropoiesis stimulating protein" means any protein that directly or indirectly causes activation of the erythropoietin receptor, for example, by binding to and causing dimerization of the receptor. Erythropoiesis stimulating proteins include erythropoietin and variants, analogs, or derivatives thereof that bind to and activate erythropoietin receptor; antibodies that bind to erythropoietin receptor and activate the

receptor; or peptides that bind to and activate erythropoietin receptor. Erythropoiesis stimulating proteins include, but are not limited to, epoetin alfa, epoetin beta, epoetin delta, epoetin omega, epoetin iota, epoetin zeta, and analogs thereof, pegylated erythropoietin, carbamylated erythropoietin, mimetic peptides (including EMP1/hematide), and mimetic antibodies. Exemplary erythropoiesis stimulating proteins include erythropoietin, darbepoetin, erythropoietin agonist variants, and peptides or antibodies that bind and activate erythropoietin receptor (and include compounds reported in U.S. Publ. Nos. 2003/0215444 and 2006/0040858, the disclosures of each of which is incorporated herein by reference in its entirety) as well as erythropoietin molecules or variants or analogs thereof as disclosed in the following patents or patent applications, which are each herein incorporated by reference in its entirety: U.S. Pat. Nos. 4,703,008; 5,441,868; 5,547,933; 5,618,698; 5,621,080; 5,756,349; 5,767,078; 5,773,569; 5,955,422; 5,830,851; 5,856,298; 5,986,047; 6,030,086; 6,310,078; 6,391,633; 6,583,272; 6,586,398; 6,900,292; 6,750,369; 7,030,226; 7,084,245; and 7,217,689; US Publ. Nos. 2002/0155998; 2003/0077753; 2003/0082749; 2003/0143202; 2004/0009902; 2004/0071694; 2004/0091961; 2004/0143857; 2004/0157293; 2004/0175379; 2004/0175824; 2004/0229318; 2004/0248815; 2004/0266690; 2005/0019914; 2005/0026834; 2005/0096461; 2005/0107297; 2005/0107591; 2005/0124045; 2005/0124564; 2005/0137329; 2005/0142642; 2005/0143292; 2005/0153879; 2005/0158822; 2005/0158832; 2005/0170457; 2005/0181359; 2005/0181482; 2005/0192211; 2005/0202538; 2005/0227289; 2005/0244409; 2006/0088906; and 2006/0111279; and PCT Publ. Nos. WO 91/05867; WO 95/05465; WO 99/66054; WO 00/24893; WO 01/81405; WO 00/61637; WO 01/36489; WO 02/014356; WO 02/19963; WO 02/20034; WO 02/49673; WO 02/085940; WO 03/029291; WO 2003/055526; WO 2003/084477; WO 2003/094858; WO 2004/002417; WO 2004/002424; WO 2004/009627; WO 2004/024761; WO 2004/033651; WO 2004/035603; WO 2004/043382; WO 2004/101600; WO 2004/101606; WO 2004/101611; WO 2004/106373; WO 2004/018667; WO 2005/001025; WO 2005/001136; WO 2005/021579; WO 2005/025606; WO 2005/032460; WO 2005/051327; WO 2005/063808; WO 2005/063809; WO 2005/070451; WO 2005/081687; WO 2005/084711; WO 2005/103076; WO 2005/100403; WO 2005/092369; WO 2006/50959; WO 2006/02646; and WO 2006/29094.

[00105] Examples of other pharmaceutical products for use with the device may include, but are not limited to, antibodies such as Vectibix® (panitumumab), Xgeva™ (denosumab) and Prolia™ (denosamab); other biological agents such as Enbrel® (etanercept, TNF-receptor /Fc fusion protein, TNF blocker), Neulasta® (pegfilgrastim, pegylated filgastrim, pegylated G-CSF, pegylated hu-Met-G-CSF), Neupogen® (filgrastim , G-CSF, hu-MetG-CSF), and Nplate® (romiplostim); small molecule drugs such as Sensipar® (cinacalcet). The device may also be used with a therapeutic antibody, a polypeptide, a protein or other chemical, such as an iron, for example, ferumoxytol, iron dextrans, ferric glyconate, and iron sucrose. The pharmaceutical product may be in liquid form, or reconstituted from lyophilized form.

[00106] Among particular illustrative proteins are the specific proteins set forth below, including fusions, fragments, analogs, variants or derivatives thereof:

[00107] OPGL specific antibodies, peptibodies, and related proteins, and the like (also referred to as RANKL specific antibodies, peptibodies and the like), including fully humanized and human OPGL specific antibodies, particularly fully humanized monoclonal antibodies, including but not limited to the antibodies described in PCT Publ. No. WO 03/002713, which is incorporated herein in its entirety as to OPGL specific antibodies and antibody related proteins, particularly those having the sequences set forth therein, particularly, but not limited to, those denoted therein: 9H7; 18B2; 2D8; 2E11; 16E1; and 22B3, including the OPGL specific antibodies having either the light chain of SEQ ID NO: 2 as set forth therein in Figure 2 and/or the heavy chain of SEQ ID NO:4, as set forth therein in Figure 4, each of which is individually and specifically incorporated by reference herein in its entirety fully as disclosed in the foregoing Publication;

[00108] Myostatin binding proteins, peptibodies, and related proteins, and the like, including myostatin specific peptibodies, particularly those described in US Publ. No. 2004/0181033 and PCT Publ. No. WO 2004/058988, which are incorporated by reference herein in their entirety particularly in parts pertinent to myostatin specific peptibodies, including but not limited to peptibodies of the mTN8-19 family, including those of SEQ ID NOS: 305-351, including TN8-19-1 through TN8-19-40, TN8-19 con1 and TN8-19 con2; peptibodies of the mL2 family of SEQ ID NOS: 357-383; the mL15 family of SEQ ID NOS: 384-409; the mL17 family of SEQ ID NOS: 410-438; the mL20 family of SEQ ID NOS: 439-446; the mL21 family of SEQ

ID NOS: 447-452; the mL24 family of SEQ ID NOS: 453-454; and those of SEQ ID NOS: 615-631, each of which is individually and specifically incorporated by reference herein in their entirety fully as disclosed in the foregoing publication;

[00109] IL-4 receptor specific antibodies, peptibodies, and related proteins, and the like, particularly those that inhibit activities mediated by binding of IL-4 and/or IL-13 to the receptor, including those described in PCT Publ. No. WO 2005/047331 or PCT Appl. No. PCT/US2004/03742 and in US Publ. No. 2005/112694, which are incorporated herein by reference in their entirety particularly in parts pertinent to IL-4 receptor specific antibodies, particularly such antibodies as are described therein, particularly, and without limitation, those designated therein: L1H1; L1H2; L1H3; L1H4; L1H5; L1H6; L1H7; L1H8; L1H9; L1H10; L1H11; L2H1; L2H2; L2H3; L2H4; L2H5; L2H6; L2H7; L2H8; L2H9; L2H10; L2H11; L2H12; L2H13; L2H14; L3H1; L4H1; L5H1; L6H1, each of which is individually and specifically incorporated by reference herein in its entirety fully as disclosed in the foregoing publication;

[00110] Interleukin 1-receptor 1 ("IL1-R1") specific antibodies, peptibodies, and related proteins, and the like, including but not limited to those described in U.S. Publ. No. 2004/097712A1, which is incorporated herein by reference in its entirety in parts pertinent to IL1-R1 specific binding proteins, monoclonal antibodies in particular, especially, without limitation, those designated therein: 15CA, 26F5, 27F2, 24E12, and 10H7, each of which is individually and specifically incorporated by reference herein in its entirety fully as disclosed in the aforementioned U.S. publication;

[00111] Ang2 specific antibodies, peptibodies, and related proteins, and the like, including but not limited to those described in PCT Publ. No. WO 03/057134 and U.S. Publ No. 2003/0229023, each of which is incorporated herein by reference in its entirety particularly in parts pertinent to Ang2 specific antibodies and peptibodies and the like, especially those of sequences described therein and including but not limited to: L1(N); L1(N) WT; L1(N) 1K WT; 2xL1(N); 2xL1(N) WT; Con4 (N), Con4 (N) 1K WT, 2xCon4 (N) 1K; L1C; L1C 1K; 2xL1C; Con4C; Con4C 1K; 2xCon4C 1K; Con4-L1 (N); Con4-L1C; TN-12-9 (N); C17 (N); TN8-8(N); TN8-14 (N); Con 1 (N), also including anti-Ang 2 antibodies and formulations such as those described in PCT Publ. No. WO 2003/030833 which is incorporated herein by reference in its entirety

as to the same, particularly Ab526; Ab528; Ab531; Ab533; Ab535; Ab536; Ab537; Ab540; Ab543; Ab544; Ab545; Ab546; A551; Ab553; Ab555; Ab558; Ab559; Ab565; AbF1AbFD; AbFE; AbFJ; AbFK; AbG1D4; AbGC1E8; AbH1C12; AblA1; AblF; AblK, AblP; and AblP, in their various permutations as described therein, each of which is individually and specifically incorporated by reference herein in its entirety fully as disclosed in the foregoing publication;

[00112] NGF specific antibodies, peptibodies, and related proteins, and the like including, in particular, but not limited to those described in US Publ. No. 2005/0074821 and US Patent No. 6,919,426, which are incorporated herein by reference in their entirety particularly as to NGF-specific antibodies and related proteins in this regard, including in particular, but not limited to, the NGF-specific antibodies therein designated 4D4, 4G6, 6H9, 7H2, 14D10 and 14D11, each of which is individually and specifically incorporated by reference herein in its entirety fully as disclosed in the foregoing publication;

[00113] CD22 specific antibodies, peptibodies, and related proteins, and the like, such as those described in US Patent No. 5,789,554, which is incorporated herein by reference in its entirety as to CD22 specific antibodies and related proteins, particularly human CD22 specific antibodies, such as but not limited to humanized and fully human antibodies, including but not limited to humanized and fully human monoclonal antibodies, particularly including but not limited to human CD22 specific IgG antibodies, such as, for instance, a dimer of a human-mouse monoclonal hLL2 gamma-chain disulfide linked to a human-mouse monoclonal hLL2 kappa-chain, including, but limited to, for example, the human CD22 specific fully humanized antibody in Epratuzumab, CAS registry number 501423-23-0;

[00114] IGF-1 receptor specific antibodies, peptibodies, and related proteins, and the like, such as those described in PCT Publ. No. WO 06/069202, which is incorporated herein by reference in its entirety as to IGF-1 receptor specific antibodies and related proteins, including but not limited to the IGF-1 specific antibodies therein designated L1H1, L2H2, L3H3, L4H4, L5H5, L6H6, L7H7, L8H8, L9H9, L10H10, L11H11, L12H12, L13H13, L14H14, L15H15, L16H16, L17H17, L18H18, L19H19, L20H20, L21H21, L22H22, L23H23, L24H24, L25H25, L26H26, L27H27, L28H28, L29H29, L30H30, L31H31, L32H32, L33H33, L34H34, L35H35, L36H36, L37H37, L38H38, L39H39, L40H40, L41H41, L42H42, L43H43, L44H44, L45H45, L46H46,

L47H47, L48H48, L49H49, L50H50, L51H51, L52H52, and IGF-1R-binding fragments and derivatives thereof, each of which is individually and specifically incorporated by reference herein in its entirety fully as disclosed in the foregoing International Publication;

[00115] Also among non-limiting examples of anti-IGF-1R antibodies for use in the methods and compositions of the present invention are each and all of those described in:

(i) US Publ. No. 2006/0040358 (published February 23, 2006), 2005/0008642 (published January 13, 2005), 2004/0228859 (published November 18, 2004), including but not limited to, for instance, antibody 1A (DSMZ Deposit No. DSM ACC 2586), antibody 8 (DSMZ Deposit No. DSM ACC 2589), antibody 23 (DSMZ Deposit No. DSM ACC 2588) and antibody 18 as described therein;

(ii) PCT Publ. No. WO 06/138729 (published December 28, 2006) and WO 05/016970 (published February 24, 2005), and Lu et al., 2004, J Biol. Chem. 279:2856-65, including but not limited to antibodies 2F8, A12, and IMC-A12 as described therein;

(iii) PCT Publ. No. WO 07/012614 (published February 1, 2007), WO 07/000328 (published January 4, 2007), WO 06/013472 (published February 9, 2006), WO 05/058967 (published June 30, 2005), and WO 03/059951 (published July 24, 2003);

(iv) US Publ. No. 2005/0084906 (published April 21, 2005), including but not limited to antibody 7C10, chimaeric antibody C7C10, antibody h7C10, antibody 7H2M, chimaeric antibody *7C10, antibody GM 607, humanized antibody 7C10 version 1, humanized antibody 7C10 version 2, humanized antibody 7C10 version 3, and antibody 7H2HM, as described therein;

(v) US Publ. Nos. 2005/0249728 (published November 10, 2005), 2005/0186203 (published August 25, 2005), 2004/0265307 (published December 30, 2004), and 2003/0235582 (published December 25, 2003) and Maloney et al., 2003, Cancer Res. 63:5073-83, including but not limited to antibody EM164, resurfaced EM164, humanized EM164, huEM164 v1.0, huEM164 v1.1, huEM164 v1.2, and huEM164 v1.3 as described therein;

(vi) US Pat. No. 7,037,498 (issued May 2, 2006), US Publ. Nos. 2005/0244408 (published November 30, 2005) and 2004/0086503 (published May 6, 2004), and

Cohen, et al., 2005, Clinical Cancer Res. 11:2063-73, e.g., antibody CP-751,871, including but not limited to each of the antibodies produced by the hybridomas having the ATCC accession numbers PTA-2792, PTA-2788, PTA-2790, PTA-2791, PTA-2789, PTA-2793, and antibodies 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2, and 4.17.3, as described therein;

(vii) US Publ. Nos. 2005/0136063 (published June 23, 2005) and 2004/0018191 (published January 29, 2004), including but not limited to antibody 19D12 and an antibody comprising a heavy chain encoded by a polynucleotide in plasmid 15H12/19D12 HCA (γ4), deposited at the ATCC under number PTA-5214, and a light chain encoded by a polynucleotide in plasmid 15H12/19D12 LCF (κ), deposited at the ATCC under number PTA-5220, as described therein; and

(viii) US Publ. No. 2004/0202655 (published October 14, 2004), including but not limited to antibodies PINT-6A1, PINT-7A2, PINT-7A4, PINT-7A5, PINT-7A6, PINT-8A1, PINT-9A2, PINT-11A1, PINT-11A2, PINT-11A3, PINT-11A4, PINT-11A5, PINT-11A7, PINT-11A12, PINT-12A1, PINT-12A2, PINT-12A3, PINT-12A4, and PINT-12A5, as described therein; each and all of which are herein incorporated by reference in their entireties, particularly as to the aforementioned antibodies, peptibodies, and related proteins and the like that target IGF-1 receptors;

[00116] B-7 related protein 1 specific antibodies, peptibodies, related proteins and the like ("B7RP-1," also is referred to in the literature as B7H2, ICOSL, B7h, and CD275), particularly B7RP-specific fully human monoclonal IgG2 antibodies, particularly fully human IgG2 monoclonal antibody that binds an epitope in the first immunoglobulin-like domain of B7RP-1, especially those that inhibit the interaction of B7RP-1 with its natural receptor, ICOS, on activated T cells in particular, especially, in all of the foregoing regards, those disclosed in U.S. Publ. No. 2008/0166352 and PCT Publ. No. WO 07/011941, which are incorporated herein by reference in their entireties as to such antibodies and related proteins, including but not limited to antibodies designated therein as follow: 16H (having light chain variable and heavy chain variable sequences SEQ ID NO:1 and SEQ ID NO:7 respectively therein); 5D (having light chain variable and heavy chain variable sequences SEQ ID NO:2 and SEQ ID NO:9 respectively therein); 2H (having light chain variable and heavy chain variable sequences SEQ ID NO:3 and SEQ ID NO:10 respectively therein); 43H (having light chain variable and heavy chain variable

sequences SEQ ID NO:6 and SEQ ID NO:14 respectively therein); 41H (having light chain variable and heavy chain variable sequences SEQ ID NO:5 and SEQ ID NO:13 respectively therein); and 15H (having light chain variable and heavy chain variable sequences SEQ ID NO:4 and SEQ ID NO:12 respectively therein), each of which is individually and specifically incorporated by reference herein in its entirety fully as disclosed in the foregoing U.S. Publication;

[00117] IL-15 specific antibodies, peptibodies, and related proteins, and the like, such as, in particular, humanized monoclonal antibodies, particularly antibodies such as those disclosed in U.S. Publ. Nos. 2003/0138421; 2003/023586; and 2004/0071702; and US Patent No. 7,153,507, each of which is incorporated herein by reference in its entirety as to IL-15 specific antibodies and related proteins, including peptibodies, including particularly, for instance, but not limited to, HuMax IL-15 antibodies and related proteins, such as, for instance, 146B7;

[00118] IFN gamma specific antibodies, peptibodies, and related proteins and the like, especially human IFN gamma specific antibodies, particularly fully human anti-IFN gamma antibodies, such as, for instance, those described in US Publ. No. 2005/0004353, which is incorporated herein by reference in its entirety as to IFN gamma specific antibodies, particularly, for example, the antibodies therein designated 1118; 1118*; 1119; 1121; and 1121*. The entire sequences of the heavy and light chains of each of these antibodies, as well as the sequences of their heavy and light chain variable regions and complementarity determining regions, are each individually and specifically incorporated by reference herein in its entirety fully as disclosed in the foregoing US Publication and in Thakur et al., Mol. Immunol. 36:1107-1115 (1999). In addition, description of the properties of these antibodies provided in the foregoing US publication is also incorporated by reference herein in its entirety. Specific antibodies include those having the heavy chain of SEQ ID NO: 17 and the light chain of SEQ ID NO:18; those having the heavy chain variable region of SEQ ID NO:6 and the light chain variable region of SEQ ID NO:8; those having the heavy chain of SEQ ID NO:19 and the light chain of SEQ ID NO:20; those having the heavy chain variable region of SEQ ID NO:10 and the light chain variable region of SEQ ID NO:12; those having the heavy chain of SEQ ID NO:32 and the light chain of SEQ ID NO:20; those having the heavy chain variable region of SEQ ID NO:30 and the light chain variable region of SEQ ID NO:12; those having the heavy chain

sequence of SEQ ID NO:21 and the light chain sequence of SEQ ID NO:22; those having the heavy chain variable region of SEQ ID NO:14 and the light chain variable region of SEQ ID NO:16; those having the heavy chain of SEQ ID NO:21 and the light chain of SEQ ID NO:33; and those having the heavy chain variable region of SEQ ID NO:14 and the light chain variable region of SEQ ID NO:31, as disclosed in the foregoing US Publication. A specific antibody contemplated is antibody 1119 as disclosed in foregoing US Publication and having a complete heavy chain of SEQ ID NO:17 as disclosed therein and having a complete light chain of SEQ ID NO:18 as disclosed therein;

[00119] TALL-1 specific antibodies, peptibodies, and the related proteins, and the like, and other TALL specific binding proteins, such as those described in U.S. Publ. Nos. 2003/0195156 and 2006/0135431, each of which is incorporated herein by reference in its entirety as to TALL-1 binding proteins, particularly the molecules of Tables 4 and 5B, each of which is individually and specifically incorporated by reference herein in its entirety fully as disclosed in the foregoing US Publications;

[00120] Parathyroid hormone ("PTH") specific antibodies, peptibodies, and related proteins, and the like, such as those described in US Patent No. 6,756,480, which is incorporated herein by reference in its entirety, particularly in parts pertinent to proteins that bind PTH;

[00121] Thrombopoietin receptor ("TPO-R") specific antibodies, peptibodies, and related proteins, and the like, such as those described in US Patent No. 6,835,809, which is herein incorporated by reference in its entirety, particularly in parts pertinent to proteins that bind TPO-R;

[00122] Hepatocyte growth factor ("HGF") specific antibodies, peptibodies, and related proteins, and the like, including those that target the HGF/SF:cMet axis (HGF/SF:c-Met), such as the fully human monoclonal antibodies that neutralize hepatocyte growth factor/scatter (HGF/SF) described in US Publ. No. 2005/0118643 and PCT Publ. No. WO 2005/017107, huL2G7 described in US Patent No. 7,220,410 and OA-5d5 described in US Patent Nos. 5,686,292 and 6,468,529 and in PCT Publ. No. WO 96/38557, each of which is incorporated herein by reference in its entirety, particularly in parts pertinent to proteins that bind HGF;

[00123] TRAIL-R2 specific antibodies, peptibodies, related proteins and the like, such as those described in US Patent No. 7,521,048, which is herein incorporated by

reference in its entirety, particularly in parts pertinent to proteins that bind TRAIL-R2;

[00124] Activin A specific antibodies, peptibodies, related proteins, and the like, including but not limited to those described in US Publ. No. 2009/0234106, which is herein incorporated by reference in its entirety, particularly in parts pertinent to proteins that bind Activin A;

[00125] PCSK9 (Proprotein Convertase Subtilisin/Kexin) specific antibodies, peptibodies, related proteins and the like including but not limited to those described in US Patent No 8,030,457, WO 11/0027287 and WO 09/026558, which are herein incorporated by reference in their entirety, particularly in parts pertinent to proteins that bind PCSK9;

[00126] TGF-beta specific antibodies, peptibodies, related proteins, and the like, including but not limited to those described in US Patent No. 6,803,453 and US Publ. No. 2007/0110747, each of which is herein incorporated by reference in its entirety, particularly in parts pertinent to proteins that bind TGF-beta;

[00127] Amyloid-beta protein specific antibodies, peptibodies, related proteins, and the like, including but not limited to those described in PCT Publ. No. WO 2006/081171, which is herein incorporated by reference in its entirety, particularly in parts pertinent to proteins that bind amyloid-beta proteins. One antibody contemplated is an antibody having a heavy chain variable region comprising SEQ ID NO: 8 and a light chain variable region having SEQ ID NO: 6 as disclosed in the International Publication;

[00128] c-Kit specific antibodies, peptibodies, related proteins, and the like, including but not limited to those described in Publ. No. 2007/0253951, which is incorporated herein by reference in its entirety, particularly in parts pertinent to proteins that bind c-Kit and/or other stem cell factor receptors;

[00129] OX40L specific antibodies, peptibodies, related proteins, and the like, including but not limited to those described in US Appl. No. 11/068,289, which is incorporated herein by reference in its entirety, particularly in parts pertinent to proteins that bind OX40L and/or other ligands of the OXO40 receptor; and

[00130] Other exemplary proteins can include Activase® (alteplase, tPA); Aranesp® (darbepoetin alfa); Epogen® (epoetin alfa, or erythropoietin); Avonex® (interferon beta-1a); Bexxar® (tositumomab, anti-CD22 monoclonal antibody);

Betaseron® (interferon-beta); Campath® (alemtuzumab, anti-CD52 monoclonal antibody); Dynepo® (epoetin delta); Velcade® (bortezomib); MLN0002 (anti- α4ß7 mAb); MLN1202 (anti-CCR2 chemokine receptor mAb); Enbrel® (etanercept, TNF-receptor /Fc fusion protein, TNF blocker); Eprex® (epoetin alfa); Erbitux® (cetuximab, anti-EGFR / HER1 / c-ErbB-1); Genotropin® (somatropin, Human Growth Hormone); Herceptin® (trastuzumab, anti-HER2/neu (erbB2) receptor mAb); Humatrope® (somatropin, Human Growth Hormone); Humira® (adalimumab); insulin in solution; Infergen® (interferon alfacon-1); Natrecor® (nesiritide; recombinant human B-type natriuretic peptide (hBNP); Kineret® (anakinra); Leukine® (sargamostim, rhuGM-CSF); LymphoCide® (epratuzumab, anti-CD22 mAb); Benlysta™ (lymphostat B, belimumab, anti-BlyS mAb); Metalyse® (tenecteplase, t-PA analog); Mircera® (methoxy polyethylene glycol-epoetin beta); Mylotarg® (gemtuzumab ozogamicin); Raptiva® (efalizumab); Cimzia® (certolizumab pegol, CDP 870); Soliris™ (eculizumab); pexelizumab (anti-C5 complement); Numax® (MEDI-524); Lucentis® (ranibizumab); Panorex® (17-1A, edrecolomab); Trabio® (lerdelimumab); TheraCim hR3 (nimotuzumab); Omnitarg (pertuzumab, 2C4); Osidem® (IDM-1); OvaRex® (B43.13); Nuvion® (visilizumab); cantuzumab mertansine (huC242-DM1); NeoRecormon® (epoetin beta); Neumega® (oprelvekin, human interleukin-11); Neulasta® (pegylated filgastrim, pegylated G-CSF, pegylated hu-Met-G-CSF); Neupogen® (filgrastim , G-CSF, hu-MetG-CSF); Orthoclone OKT3® (muromonab-CD3, anti-CD3 monoclonal antibody); Procrit® (epoetin alfa); Remicade® (infliximab, anti-TNFα monoclonal antibody); Reopro® (abciximab, anti-GP lIb/Ilia receptor monoclonal antibody); Actemra® (anti-IL6 Receptor mAb); Avastin® (bevacizumab), HuMax-CD4 (zanolimumab); Rituxan® (rituximab, anti-CD20 mAb); Tarceva® (erlotinib); Roferon-A®-(interferon alfa-2a); Simulect® (basiliximab); Prexige® (lumiracoxib); Synagis® (palivizumab); 146B7-CHO (anti-IL15 antibody, see US Patent No. 7,153,507); Tysabri® (natalizumab, anti-α4integrin mAb); Valortim® (MDX-1303, anti-B. anthracis protective antigen mAb); ABthrax™; Vectibix® (panitumumab); Xolair® (omalizumab); ETI211 (anti-MRSA mAb); IL-1 trap (the Fc portion of human IgG1 and the extracellular domains of both IL-1 receptor components (the Type I receptor and receptor accessory protein)); VEGF trap (Ig domains of VEGFR1 fused to IgG1 Fc); Zenapax® (daclizumab); Zenapax® (daclizumab, anti-IL-2Rα

mAb); Zevalin® (ibritumomab tiuxetan); Zetia® (ezetimibe); Orencia® (atacicept, TACI-Ig); anti-CD80 monoclonal antibody (galiximab); anti-CD23 mAb (lumiliximab); BR2-Fc (huBR3 / huFc fusion protein, soluble BAFF antagonist); CNTO 148 (golimumab, anti-TNFα mAb); HGS-ETR1 (mapatumumab; human anti-TRAIL Receptor-1 mAb); HuMax-CD20 (ocrelizumab, anti-CD20 human mAb); HuMax-EGFR (zalutumumab); M200 (volociximab, anti-α5β1 integrin mAb); MDX-010 (ipilimumab, anti-CTLA-4 mAb and VEGFR-1 (IMC-18F1); anti-BR3 mAb; anti-C. difficile Toxin A and Toxin B C mAbs MDX-066 (CDA-1) and MDX-1388); anti-CD22 dsFv-PE38 conjugates (CAT-3888 and CAT-8015); anti-CD25 mAb (HuMax-TAC); anti-CD3 mAb (NI-0401); adecatumumab; anti-CD30 mAb (MDX-060); MDX-1333 (anti-IFNAR); anti-CD38 mAb (HuMax CD38); anti-CD40L mAb; anti-Cripto mAb; anti-CTGF Idiopathic Pulmonary Fibrosis Phase I Fibrogen (FG-3019); anti-CTLA4 mAb; anti-eotaxin1 mAb (CAT-213); anti-FGF8 mAb; anti-ganglioside GD2 mAb; anti-ganglioside GM2 mAb; anti-GDF-8 human mAb (MYO-029); anti-GM-CSF Receptor mAb (CAM-3001); anti-HepC mAb (HuMax HepC); anti-IFNα mAb (MEDI-545, MDX-1103); anti-IGF1R mAb; anti-IGF-1R mAb (HuMax-Inflam); anti-IL12 mAb (ABT-874); anti-IL12/IL23 mAb (CNTO 1275); anti-IL13 mAb (CAT-354); anti-IL2Ra mAb (HuMax-TAC); anti-IL5 Receptor mAb; anti-integrin receptors mAb (MDX-018, CNTO 95); anti-IP10 Ulcerative Colitis mAb (MDX-1100); anti-LLY antibody; BMS-66513; anti-Mannose Receptor/hCGβ mAb (MDX-1307); anti-mesothelin dsFv-PE38 conjugate (CAT-5001); anti-PD1mAb (MDX-1106 (ONO-4538)); anti-PDGFRα antibody (IMC-3G3); anti-TGFß mAb (GC-1008); anti-TRAIL Receptor-2 human mAb (HGS-ETR2); anti-TWEAK mAb; anti-VEGFR/Flt-1 mAb; anti-ZP3 mAb (HuMax-ZP3); NVS Antibody #1; and NVS Antibody #2.

[00131] In addition to any of the foregoing, exemplary antibodies may also include a sclerostin antibody, such as but not limited to romosozumab, blosozumab, or BPS 804 (Novartis). Also included can be therapeutics such as rilotumumab, bixalomer, trebananib, ganitumab, conatumumab, motesanib diphosphate, brodalumab, vidupiprant, panitumumab, denosumab, NPLATE, PROLIA, VECTIBIX or XGEVA. Additionally, included in the device can be a monoclonal antibody (IgG) that binds human Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9), e.g. U.S. Patent No. 8,030,547, U.S. Publ. No. 13/469,032, or any of the following PCT Publ.

Nos. WO2008/057457, WO2008/057458, WO2008/057459, WO2008/063382, WO2008/133647, WO2009/100297, WO2009/100318, WO2011/037791, WO2011/053759, WO2011/053783, WO2008/125623, WO2011/072263, WO2009/055783, WO2012/0544438, WO2010/029513, WO2011/111007, WO2010/077854, WO2012/088313, WO2012/101251, WO2012/101252,WO2012/101253, WO2012/109530, and WO2001/031007, each of which (U.S. and PCT) is incorporated herein by reference in its entirety, particularly in parts pertinent to proteins that bind PCSK9.

We claim:

1. An injector comprising:

a container including a wall with an interior surface and a seal assembly with an interior surface, the interior surfaces of the wall and the seal assembly defining a closed sterile reservoir filled with a drug product;

a fluid delivery system comprising a sterile container needle having a point disposed only partially through the seal assembly in a storage state, and disposed through the interior surface of the seal assembly into the sterile reservoir in a delivery state; and

an actuator that is adapted to move the container needle from the storage state to the delivery state.

2. The injector of claim 1, wherein the wall of the container comprises a rigid wall.

3. The injector of claim 1, wherein the wall of the container comprises a flexible wall.

4. The injector of any one of claims 1 to 3, wherein the seal assembly consists of a flexible unitary wall having an interior surface that defines the interior surface of the seal assembly.

5. The injector of claim 4, wherein the flexible unitary wall defines a septum disposed across the opening and fixedly attached to the wall of the container.

6. The injector of claim 4, wherein the wall of the container defines a bore, and the unitary flexible wall defines a stopper that is moveable along the bore.

7. The injector of claim 6, wherein the wall of the container defines a closed end opposite the stopper and an open end in which the stopper is disposed.

8. The injector of claim 4, wherein the wall of the container defines a bore with an opening in fluid communication with a first end of the bore, and the unitary flexible wall defines a septum disposed across the opening and fixedly attached to the wall of the container, the container further comprising a stopper that is disposed within a second end of the bore and is moveable along the bore.

9. The injector of any one of claims 1 to 3, wherein the seal assembly comprises a flexible wall with an interior surface that defines the interior surface of the seal assembly, and a barrier disposed exterior of the flexible wall to define an enclosed space between the flexible wall and the clean barrier, the point of the container needle disposed through the barrier into the space in the storage state.

10. The injector of claim 9, wherein the wall of the container defines a bore, and the flexible wall and the barrier each define a stopper that is moveable along the bore.

11. The injector of claim 9, wherein the container comprises a vent in fluid communication with the space between the barrier and the flexible wall.

12. The injector of claim 11, wherein the vent is formed in the barrier.

13. The injector of claim 11, wherein the vent is formed within the interior surface of the wall of the container.

14. The injector of claim 9, wherein the wall of the container defines a closed end opposite the stoppers and an open end in which the stoppers are disposed.

15. The injector of claim 9, wherein the wall of the container defines a bore with an opening in fluid communication with a first end of the bore, and the flexible wall and the barrier each defines a septum disposed across the opening and fixedly attached to the wall of the container, the container further comprising a stopper that is disposed within a second end of the bore and is moveable along the bore.

16. The injector of any one of claims 1 to 15, wherein the fluid delivery system comprises sterile flexible tubing connected at a first end to the container needle and a second end to a sterile injection needle received within a sterile cover that closes off the sterile injection needle.

17. The injector of any one of claims 1 to 16, wherein the actuator is adapted to delay movement of the container needle from the storage state to the delivery state after an input is received.

18. The injector of any one of claims 1 to 17, further comprising a mechanical, electro-mechanical, or electrical input device coupled to the actuator.

19. An injector comprising:

a container including a wall with an interior surface defining a closed sterile reservoir filled with a drug product;

a sterile fluid delivery system in fluid communication with the sterile reservoir in a delivery state, the fluid delivery system either in fluid communication or not in fluid communication in a storage state; and

a clean assembly comprising a remainder of the injector in which the container and the fluid delivery system are disposed.

20. The injector of any one of claims 1 to 19, wherein the drug product comprises a volume of an erythropoiesis stimulating agent.

21. The injector of any one of claims 1 to 19, wherein the drug product comprises a volume of a granulocyte colony-stimulating factor.

22. The injector of any one of claims 1 to 19, wherein the drug product comprises a volume of a TNF blocker.

23. The injector of any one of claims 1 to 19, wherein the drug product comprises a volume of a pegylated granulocyte colony-stimulating factor.

24. The injector of any one of claims 1 to 19, wherein the drug product comprises a volume of interleukin-receptor specific antibody.

25. The injector of any one of claims 1 to 19, wherein the drug product comprises a volume of IGF-receptor (Insulin Growth Factor receptor) specific antibody.

26. The injector of any one of claims 1 to 19, wherein the drug product comprises a volume of TGF-specific antibody.

27. The injector of any one of claims 1 to 19, wherein the drug product comprises a volume of PCSK9 (Proprotein Convertase Subtilisin/Kexin Type 9) - specific antibody.

28. A method of assembling an injector, the method comprising:

filling a sterile reservoir of a container with a drug product under sterile conditions, the reservoir defined by an interior surface of a wall of the container;

attaching a sterile fluid delivery system to the container under sterile conditions, the fluid delivery system in fluid communication with the reservoir in a delivery state and either in fluid communication or not in fluid communication with the reservoir in a storage state; and

assembling the remainder of the injector under clean room conditions.

29. The method of claim 28, wherein assembling the remainder of the injector comprises:

attaching the fluid delivery system to an actuator under clean room conditions, the actuator adapted to change the state of the fluid delivery system from the storage state to a delivery state.

30. A method of assembling an injector, the method comprising:

filling a sterile reservoir of a container with a drug product under sterile conditions, the reservoir defined by an interior surface of a wall of the container and attached to a sterile fluid delivery system, the fluid delivery system in fluid communication with the reservoir in a delivery state and either in fluid communication or not in fluid communication with the reservoir in a storage state; and

assembling the remainder of the injector under clean room conditions.

31. The method of claim 30, wherein assembling the remainder of the injector comprises:

attaching the fluid delivery system to an actuator under clean room conditions, the actuator adapted to change the state of the fluid delivery system from the storage state to a delivery state..