A METHOD OF INSERTING A LUBRICANT FREE STOPPER INTO A LUBRICANT FREE BARREL OR A LUBRICANT FREE CARTRIDGE TUBE AND A SYSTEM FOR ASSEMBLING SAME

FIELD

[0001] The present invention relates generally to syringes and syringe assemblies, and more particularly, to a method for the insertion of a lubricant free stopper into a lubricant free barrel (*e.g.*, syringe) or a lubricant free cartridge tube (*e.g.*, cartridge). A system for assembling a lubricant free syringe and a lubricant free cartridge is also provided.

BACKGROUND

[0002] Pre-filled syringes function to both store and deliver drugs and or biologics (*e.g.*, pharmaceutical and/or biopharmaceutical treatments). Also, pre-filled syringes generally offer cost savings to the pharmaceutical industry and may improve the safety, convenience, and efficacy of drug delivery. Biopharmaceuticals are an important class of pharmaceuticals that may increase the use of pre-filled syringes and related devices, such as auto injectors or injectable pens (*e.g.*, EpiPen®). Non-limiting examples of biopharmaceuticals include insulin, vaccines, antibodies, blood products, hormones, and/or cytokines. As more pharmaceuticals and particularly biopharmaceuticals are utilized for delivery in pre-filled syringes and other pre-filled injection devices, difficulties regarding the use of conventional syringe technology in pre-filled injection devices became apparent.

[0003] There are several aspects of traditional syringe construction that present a challenge for their use as pre-filled syringes. One is the use of silicone (*e.g.*, silicone oil) and/or other lubricants. Conventionally, silicone provides a liquid seal between the stopper and the syringe barrel. While silicone has traditionally been used to ensure that the force required to actuate a pre-filled syringe or similar pre-filled injectable device is minimized, the use of silicone as a lubricant poses a contamination risk. For example, silicone may degrade or contaminate the drug or biologic within the injectable device. Additionally, the silicone may be injected into a patient along with the drug. Silicone

may be of particular concern regarding biopharmaceuticals because it can cause aggregation of certain proteins, thereby rendering the biopharmaceutical unusable for injection.

[0004] A second aspect is the occurrence of small bumps or asperities on the inner surface of the insertion tube that may be present as a by-product of the insertion tube manufacturing process. Typically, these asperities have no effect on a stopper as the silicone in the insertion tube allows the stopper to pass over the asperities without issue. However, if silicone or another suitable lubricant is not applied or is inadvertently omitted, damage or destruction of the stopper may cause failure in the syringe or similar injectable device.

[0005] Therefore, a need exists for a method of inserting a lubricant free stopper into a lubricant free barrel or a lubricant free cartridge tube in a manner that both reduces the potential for drug contamination and minimizes damage to the stopper.

SUMMARY

[0006] According to one Aspect ("Aspect 1"), a method for inserting a lubricant free stopper into a lubricant free barrel includes (A) inserting a stopper that includes at least one sealing rib into a placement region located at a proximal end of an insertion tube, the insertion tube having a body connected to the placement region through a transition zone, (B) lowering the body of the insertion tube into a syringe barrel having a barrel flange to a position located past the barrel flange, (C) maneuvering the stopper to a distal opening of the insertion tube using an insertion pin, (D) retracting the insertion tube while the stopper remains in a fixed position within the syringe barrel by the insertion pin, where the stopper is securely positioned within the syringe barrel and (E) fully retracting the insertion pin and the insertion tube from the barrel to form a stoppered syringe. At least the stopper, the insertion tube, the body of the insertion tube, the syringe barrel, the barrel flange, and the insertion pin are free or substantially free of lubricants.

[0007] According to another Aspect ("Aspect 2") further to Aspect 1, the insertion tube has an average surface roughness (Sa) from about 20 nm to about 400 nm.

[0008] According to another Aspect ("Aspect 3") further to Aspects 1 and 2, the body of the insertion tube has an average kurtosis (S_{ku}) less than about 8.

[0009] According to another Aspect ("Aspect 4") further to any of the preceding Aspects, the stopper is inserted into the insertion tube at a peak insertion force ranging from about 10 N to about 200 N.

[0010] According to another Aspect ("Aspect 5") further to any of the preceding Aspects, the stopper includes at least one sealing rib and the sealing rib has a line count of less than 30.

[0011] According to another Aspect ("Aspect 6") further to any of the preceding Aspects, the stoppered syringe has a helium leak rate that is not greater than 6×10^{-6} sccs.

[0012] According to another Aspect ("Aspect 7") further to any of the preceding Aspects, step (A) and step (B) occur sequentially or simultaneously.

[0013] According to another Aspect ("Aspect 8") further to any of the preceding Aspects, in step (B), a gap is located between the insertion tube and an inner surface of the barrel to allow for pressure venting.

[0014] According to another Aspect ("Aspect 9") further to any of the preceding Aspects, in step (D) the insertion tube is retracted prior to the insertion pin.

[0015] According to another Aspect ("Aspect 10") further to any of the preceding Aspects, in step (E) the insertion tube and the insertion pin are retracted sequentially or simultaneously.

[0016] According to another Aspect ("Aspect 11") further to any of the preceding Aspects, the stopper comprises an elastomeric body and a polymer layer thereon.

[0017] According to another Aspect ("Aspect 12") further to Aspect 11, the expanded fluoropolymer includes an expanded fluoropolymer.

[0018] According to another Aspect ("Aspect 13") further to Aspect 12, the expanded fluoropolymer includes an expanded polytetrafluoroethylene.

[0019] According to another Aspect ("Aspect 14") further to any of the preceding Aspects, a therapeutic compound is delivered to the syringe barrel prior to lowering the insertion tube into the syringe barrel.

[0020] According to another Aspect ("Aspect 15") further to any of the preceding Aspects, the therapeutic substance contains therein a biologic, a therapeutic compound, or a combination thereof.

[0021] According to another Aspect ("Aspect 16") further to any of the preceding Aspects, an amount of particles in the barrel is less than about 600 particles / mL for particles greater than 10 μm in size when measured in water for injection (WFI).

[0022] According to another Aspect ("Aspect 17") further to any of the preceding Aspects, an amount of particles in the barrel is less than 60 particles /mL for particles greater than 25 μm in size when measured in water for injection (WFI).

[0023] According to another Aspect ("Aspect 18") further to any of the preceding Aspects, the insertion tube has been electropolished, extrude honed, or a combination thereof.

[0024] According to another Aspect ("Aspect 19"), a system includes an (A) insertion tube having (1) a placement region having a diameter for receiving a stopper from a stopper feeder, (2) a body having a diameter that is smaller than the diameter of the placement region, and (3) a transition zone having a tapered angle for transitioning the stopper from the placement region to the insertion tube body, (B) an insertion pin for maneuvering the stopper through the insertion tube, and (C) a barrel having an inner surface for receiving the stopper from the insertion tube and a therapeutic substance from a therapeutic feeder. (A) to (C) include a system to form a pre-filled syringe or pre-filled cartridge and the system, the pre-filled syringe, and the pre-filled cartridge are lubricant free or substantially lubricant free.

[0025] According to another Aspect ("Aspect 20") further to Aspect 19, the taper angle is between about 1 degree and about 20 degrees.

[0026] According to another Aspect ("Aspect 21") further to Aspects 19 and 20, the insertion tube has an average surface roughness (Sa) from about 20 nm to about 400 nm.

[0027] According to another Aspect ("Aspect 22") further to Aspects 19-21, the insertion tube body has an average kurtosis (Sku) less than about 8.

[0028] According to another Aspect ("Aspect 23") further to Aspects 19-22, the insertion tube has been electropolished, extrude honed, or a combination thereof.

[0029] According to another Aspect ("Aspect 24") further to Aspects 19-23, the therapeutic substance contains therein a biologic, a therapeutic compound, or a combination thereof.

[0030] According to another Aspect ("Aspect 25") further to Aspects 19-24, the stopper comprises an elastomeric body and a polymer layer at least partially covering the elastomeric body.

[0031] According to another Aspect ("Aspect 26") further to Aspect 25, the polymer layer comprises an expanded fluoropolymer.

[0032] According to another Aspect ("Aspect 27") further to Aspect 26, the expanded fluoropolymer comprises an expanded polytetrafluoroethylene.

[0033] According to another Aspect ("Aspect 28"), a method for inserting a lubricant free stopper into a lubricant free cartridge tube includes (A) inserting a stopper that includes at least one sealing rib into a placement region located at a proximal end of an insertion tube, the insertion tube having a body connected to the placement region through a transition zone, (B) lowering the body of the insertion tube into a cartridge tube having an end portion to a position located past the top of the cartridge tube, (C) maneuvering the stopper to a distal opening of the insertion tube using an insertion pin, (D) retracting the insertion tube while the stopper remains in a fixed position within the cartridge tube by the insertion pin, where the stopper is securely positioned within the cartridge tube, and (E) fully retracting the insertion pin and the insertion tube from the cartridge tube to form a stoppered cartridge. At least the stopper, the insertion tube, the body of the insertion tube, the cartridge tube, the top of the cartridge tube, and the insertion pin are free or substantially free of lubricants.

[0034] According to another Aspect ("Aspect 29") further to Aspect 28, the stopper is inserted into the insertion tube at a peak insertion force ranging from about 10 N to about 200 N.

[0035] According to another Aspect ("Aspect 30") further to Aspects 28 and 29, the stopper includes at least one sealing rib and the sealing rib has a line count of less than 30.

[0036] According to another Aspect ("Aspect 31") further to Aspects 28-30, (A) and step (B) occur sequentially or simultaneously.

[0037] According to another Aspect ("Aspect 32") further to Aspects 28-31, in step (B), a gap is located between the insertion tube and an inner surface of the cartridge tube to allow for pressure venting.

[0038] According to another Aspect ("Aspect 33") further to Aspects 28-32, in step (D) the insertion tube is retracted prior to the insertion pin.

[0039] According to another Aspect ("Aspect 34") further to Aspects 28-33, in step (E) the insertion tube and the insertion pin are retracted sequentially or simultaneously.

[0040] According to another Aspect ("Aspect 35") further to Aspects 28-34, the stopper comprises an elastomeric body and a polymer layer thereon.

[0041] According to another Aspect ("Aspect 36") further to Aspect 35, the polymer layer comprises an expanded fluoropolymer.

[0042] According to another Aspect ("Aspect 37") further to Aspect 36, the expanded fluoropolymer comprises an expanded polytetrafluoroethylene.

[0043] According to another Aspect ("Aspect 38") further to Aspects 28-37, further including delivering a therapeutic compound to the cartridge tube prior to lowering the insertion tube into the cartridge tube.

[0044] According to another Aspect ("Aspect 39") further to Aspect 38, the therapeutic substance contains therein a biologic, a therapeutic compound, or a combination thereof.

[0045] According to another Aspect ("Aspect 40") further to Aspects 28-39, the insertion tube has been electropolished, extrude honed, or a combination thereof.

[0046] According to another Aspect ("Aspect 41") further to Aspects 28-40, the insertion tube has an average surface roughness (Sa) from about 20 nm to about 400 nm.

[0047] According to another Aspect ("Aspect 42") further to Aspects 28-41, the body of the insertion tube has an average kurtosis (S_{ku}) less than about 8.

[0048] According to another Aspect ("Aspect 43") further to Aspects 28-42, the stoppered syringe has a helium leak rate that is not greater than 6×10^{-6} sccs.

BRIEF DESCRIPTION OF THE DRAWINGS

[0049] The accompanying drawings are included to provide a further understanding of the disclosure and are incorporated in and constitute a part of this specification, illustrate embodiments, and together with the description serve to explain the principles of the disclosure.

[0050] FIG. 1A is a schematic illustration of a syringe in accordance with some embodiments;

[0051] FIG. 1B is a schematic illustration of a cartridge in accordance with some embodiments;

[0052] FIG. 2 is a schematic illustration depicting the head space between a stopper and the liquid in a barrel or cartridge tube in accordance with some embodiments;

[0053] FIG. 3 is a schematic illustration of a cutaway view of a stopper having thereon a polymer layer in accordance with some embodiments;

[0054] FIG. 4 is a schematic illustration of a cutaway view of a stopper having thereon a laminate in accordance with some embodiments;

[0055] FIG. 5A is an isometric view of an insertion tube according to some embodiments;

[0056] FIG. 5B is a cross-sectional view of the insertion tube of FIG. 5A ;

[0057] FIG. 6A is an isometric view of an insertion pin in accordance with some embodiments;

[0058] FIG. 6B is a cross-sectional view of the insertion pin of FIG. 6A;

[0059] FIG. 6C is a cross-sectional view of another insertion pin in accordance with some embodiments;

[0060] FIGS. 7A-7E depict an exemplary insertion method utilizing an insertion tube in conjunction with an insertion pin to insert a lubricant free stopper in a lubricant free syringe barrel in accordance with some embodiments;

[0061] FIGS. 8A-8E depict an exemplary insertion method utilizing an insertion tube in conjunction with an insertion pin to insert a lubricant free stopper in a lubricant free cartridge tube in accordance with some embodiments; and

[0062] FIG. 9 depicts a system for assembling a lubricant free pre-filled syringe or cartridge.

DETAILED DESCRIPTION

[0063] Persons skilled in the art will readily appreciate that various aspects of the present disclosure can be realized by any number of methods and apparatus configured to perform the intended functions. It should also be noted that the accompanying drawing figures referred to herein are not necessarily drawn to scale, but may be exaggerated to illustrate various aspects of the present disclosure, and in that regard, the figures should not be construed as limiting. The terms "barrel" and "syringe barrel" may be used interchangeably herein. It is to be appreciated that the terms "non-lubricated" and "lubricant free" may be interchangeably used herein. It is to be noted that the phrase "non-lubricated syringe barrel" and "non-lubricated barrel" may be interchanged with the phrase "non-lubricated cartridge tube" within this disclosure.

[0064] The present disclosure is directed to a method of inserting a stopper having thereon a polymer layer (*e.g.*, an expanded fluoropolymer layer) into a lubricant free barrel or lubricant free cartridge tube through the use of an insertion tube and an insertion pin. The stopper further includes an elastomeric body and the polymer layer that at least partially covers the elastomeric body. The syringe or cartridge may be pre-filled for storing and delivering a drug or biologic to a patient. As used herein, the term "syringe" or "cartridge" is meant to refer to any device that delivers at least one therapeutic compound (*e.g.*, drug or biologic) via injection with a needle or with a "needleless" system (*e.g.*, a luer system). The syringe or cartridge may be used to administer different therapeutic compounds such as, for example, drugs and biologics, including but not limited to, antibodies, antisense, RNA interference, gene therapy, primary and embryonic stem cells, vaccines, and combinations thereof. The disclosure hereafter equally applies to a syringe or to a cartridge. Numerous types of medical delivery devices are contemplated, such as, for example, a syringe, an auto-injector, or injectable pen, and are considered to be within the purview of the present disclosure.

[0065] As shown in FIG. 1A, the syringe 10 may include a barrel 20 with an inner surface 25 and a piercing element (*e.g.*, needle) 30 for injecting a therapeutic compound(s). The plunger 50 is formed of a stopper 40 that may be affixed to an end of a plunger rod 85. In some embodiments, the stopper is not attached to the plunger

rod 85. The stopper 40 contacts at least a portion of the inner surface 25 of the barrel 20 via one or more ribs 42, 44. Although two ribs 42, 44 are shown in FIG. 1A, any number of ribs may be present on the stopper 40 as long as there is at least one sealing rib, such as the front sealing rib 42. In this embodiment, rib 44 may also be a sealing rib. Hereafter, ribs 42, 44 will both be referred to as sealing ribs for ease of discussion. Sealing ribs provide container closure integrity to a pre-filled syringe or cartridge. One or more flanges 70 may be used as a finger grip for pressing and translating the plunger 50 within the barrel 20. In some embodiments, the stopper 40 includes opposed proximal and distal ends 90, 95 and a side surface 115 extending therebetween. The side surface 115 of stopper 40 may include one or more sealing rib(s), such as one or more circumferentially extending annular ribs. Turning to FIG. 1B, in a cartridge 35, the plunger rod (not shown) and the stopper 40 are not attached. The stopper 40 contacts at least a portion of the inner surface 25 of the cartridge tube 32 via one or more ribs, such as sealing rib 42. In addition, the needle (not shown) is separate from the cartridge tube 32. Rather than a needle, the cartridge 35 contains a sealed cap 34. It is to be appreciated that the components of the syringe 10 and the cartridge 35 are lubricant free or substantially lubricant free.

[0066] Turning to FIG. 2, in some embodiments, the stopper 40 is inserted at a specific, desired location within the barrel 20. The phrase “barrel 20” may be interchanged with “cartridge tube 32” herein. This specific location is a predetermined height above the liquid surface 60 of the therapeutic solution 55 in the barrel 20. The therapeutic solution 55 can have a liquid height H1. H1 is a function of the amount of therapeutic solution 55 located within the barrel 20, which, in turn, depends on the volume of the therapeutic substance to be administered. In some embodiments, the location of the stopper 40 within the barrel allows for a specific amount of “headspace” H2. As used herein, “headspace” is meant to describe the height from the top of the liquid surface 60 to the front edge 45 of the front sealing rib 42 of the stopper 40. Sealing rib 44 is shown for illustrative purposes only. In some embodiments, the headspace H2 is minimized to reduce the amount of air in the barrel 20 that might be injected into a patient, for drug stability, and/or for shipping purposes.

[0067] In some embodiments, after insertion of the stopper 40 using the method described herein, the headspace height H2 is less than about 25 mm, less than about 23 mm, less than about 21 mm, less than about 19 mm, less than about 17 mm, less than about 15 mm, less than about 13 mm, less than about 10 mm, less than about 8 mm, less than about 5 mm, less than about 3 mm, less than about 2 mm, less than about 1 mm, or less than about 0.5 mm. In some embodiments, headspace H2 may range from about 1 mm to about 25 mm, from about 1 mm to about 23 mm, from about 1 mm to about 21 mm, from about 1 mm to about 19 mm, from about 1 mm to about 17 mm, from about 1 mm to about 15 mm, from about 1 mm to about 13 mm, from about 1 mm to about 10 mm, from about 1 mm to about 8 mm, from about 1 mm to about 5 mm, from about 1 mm to about 3 mm, from about 1 mm to about 2 mm, from about 0.5 mm to about 2 mm, or from about 0.5 mm to about 1 mm.

[0068] The barrel 20 or cartridge tube 32 may be formed of a hard material, such as a glass material (*e.g.*, borosilicate glass), a ceramic material, one or more polymeric materials (e.g., polypropylene, polyethylene, and copolymers thereof), a metallic material, a plastic material (e.g., cyclic olefin polymers and cyclic olefin copolymers), and combinations thereof. In certain embodiments, the barrel 20 or cartridge tube 32 may be formed of glass, resin, plastic, or metal without any lubricants (*e.g.*, silicone) present on the inner surface 25 of the barrel 20 or cartridge tube 32.

[0069] The stopper 40 is formed of an elastomeric body at least partially covered by a polymer (*e.g.*, an expanded polymer). In some embodiments, the elastomeric body may have thereon one or more polymer or expanded polymer layers. For example, FIG. 3 illustrates a stopper 40 that has an elastomeric body 125 and a single layer of a polymer or expanded polymer 140 at least partially covering the elastomeric body 125. In another embodiment depicted in FIG. 4, the stopper 40 includes an elastomeric body 125 and a laminate layer 130 that may be formed of a polymer or expanded polymer 140 (*e.g.* an expanded fluoropolymer) and a porous layer 150 (*e.g.,* fluorinated ethylene propylene (FEP)). As discussed above, the stopper 40 may have one or more sealing ribs, such as sealing ribs 42, 44, extending therefrom.

[0070] In some embodiments, the expanded polymer is an expanded fluoropolymer. Examples of fluoropolymers that may be utilized as a polymer or expanded polymer 140

or as the porous layer 150 include, but are not limited to, polytetrafluoroethylene (PTFE), expanded polytetrafluoroethylene (ePTFE), densified expanded polytetrafluoroethylene (ePTFE), densified polytetrafluoroethylene (PTFE), expanded modified PTFE, expanded copolymers of PTFE, ethylene-(perfluoro-ethylene-propene) copolymer (EFEP), polyvinylidene difluoride (PVDF), fluorinated ethylene propylene (FEP), perfluoroalkoxy copolymer resin (PFA), polyvinylfluoride, perfluoropropylevinylether, and perfluoroalkoxy polymers. Patents have been granted on expandable blends of PTFE, expandable modified PTFE, and expandable copolymers of PTFE, such as, but not limited to, U.S. Patent No. 5,708,044 to Branca; U.S. Patent No. 6,541,589 to Baillie; U.S. Patent No. 7,531,611 to Sabol *et al.*; U.S. Patent No. 8,637,144 to Ford; and U.S. Patent No. 9,139,669 to Xu *et al*. Non-fluoropolymers such as polyethylene, polypropylene, and polycarbonate may also be utilized as a polymer or expanded polymer layer 140.

[0071] Non-limiting examples of elastomers that can be used to form the elastomeric body 125 include any elastomer suitable for the application, most notably rubbers constructed from butyl, bromobutyl, chlorobutyl, silicone, nitrile, styrene butadiene, polychloroprene, ethylene propylene diene, fluoroelastomers, thermoplastic elastomers (TPE), thermoplastic vulcanizates (TPV), and combinations and blends thereof. In some embodiments, the elastomeric body 125 may have an initial modulus ranging from about 2.5 MPa to about 5 MPa. In some embodiments, the elastomeric body 125 may have an initial modulus between about 3 MPa to about 4 MPa. In one non-limiting embodiment, the initial modulus may be, for example, about 3.5 MPa.

[0072] The laminate layer 130 may have a thicknesses less than about 30 microns. In some embodiments, the thickness of the laminate layer 130 may range from about 0.5 microns to about 20 microns. The membrane forming the polymer or expanded polymer layer 140 (FIG. 3) and/or the porous layer 150 (FIG. 4) may be pre-treated or post-treated with chemical etching, plasma treating, corona treatment, roughening, or the like to improve the bonding of the polymer or expanded polymer layer 140 and/or the porous layer 150 to the elastomeric body 125. The materials of the laminate layer 130 and polymer or expanded polymer layer 140 are chosen to provide a low coefficient of friction, compliance, low extractables and leachables, good barrier properties as they

relate to extractables and leachables from the elastomeric body 125, as well as good air and liquid impermeability.

[0073] In another embodiment, the polymer or expanded polymer layer 140 may be used with non-elastomeric materials such as, but not limited to plastics (*e.g.,* polypropylene, polycarbonate, and polyethylene), thermoplastics, and fluoropolymer materials such ethylene-(perfluoro-ethylene-propene) copolymer (EFEP), polyvinylidene difluoride (PVDF), and perfluoroalkoxy polymer resin (PFA).

[0074] In some embodiments, an insertion tube and an insertion pin may be used in combination to insert a lubricant free stopper into a non-lubricated syringe barrel or non-lubricated cartridge tube 32 with little to no distortion, buckling, or wrinkling of the stopper. Turning to FIGS. 5A and 5B, an exemplary insertion tube 1000 is shown. The insertion tube 1000 allows a non-lubricated stopper to be placed inside a non-lubricated syringe barrel or non-lubricated cartridge tube without over-pressurizing the liquid contained therein. As shown in FIGS. 5A and 5B, the insertion tube 1000 has a proximal end 1012 and a distal end 1014. The insertion tube 1000 also includes a body 1010 and a machine adaptor 1020. An alignment flange 1030 protrudes from the end of the machine adaptor 1020. The alignment flange 1030 has a shape that is sufficient to align with auxiliary equipment on a conventional syringe filling line (not depicted). The body 1010 is the portion of the insertion tube 1000 that fits within a syringe barrel and allows a stopper to be placed into a syringe barrel or cartridge tube. The outer diameter D1 of the body 1010 is sized smaller than the inner diameter of the syringe barrel or cartridge tube to allow air space between the outside of the insertion tube body 1010 and a syringe barrel or cartridge tube during insertion (shown in FIG. 7C and FIG. 8C).

[0075] The transition zone 1040 is where the stopper is compressed to a diameter D2 that is sufficient to pass through the distal opening 1050 of the insertion tube 1000. Thus, the diameter of the stopper (not shown) is reduced from D3 (*i.e.*, the diameter of the placement region 1042) to D2 (*i.e.*, the diameter at the distal end of the transition zone 1040). The transition zone 1040 tapers from the placement region 1042 to the body 1010 at a taper angle (B). The placement region 1042 has a diameter D3 from about 3 mm to about 20 mm, about 5 mm to about 15 mm, from about 7 mm to about 10 mm, from about 7 mm to about 8 mm, or from about 7.5 mm to about 8 mm. The taper

angle (B) may range from about 1 degree to about 20 degrees, from about 5 degrees to about 20 degrees, from about 1 degree to about 15 degrees, from about 2 degrees to about 15 degrees, from about 3 degrees to about 15 degrees, from about 4 degrees to about 15 degrees, from about 5 degrees to about 15 degrees, from about 1 degree to 10 degrees, or from about 5 degrees to about 10 degrees.

[0076] FIGS. 6A, 6B, and 6C illustrate an insertion pin 600 (FIGS. 6A and B) and an insertion pin 605 (FIG. 6C) that may be used in combination with an insertion tube, such as the insertion tube 1000 illustrated in FIGS. 5A and 5B, to insert a stopper into a barrel or cartridge tube. The insertion pins 600 and 605 include a cylindrical body 602 having a proximal end 606 and a distal end 608. The pin tip end 610 of insertion pin 600 is connected to the cylindrical body 602 and interfaces with the cavity of the stopper (not shown). The distal end 608 may be sized to mate with a machine adapter (not shown) used to push the insertion pin 600 and insertion pin 605 through an insertion tube, such as the insertion tube 1000 shown in FIGS. 5A and FIG 5B.

[0077] The cylindrical body 602 has a diameter D4 that is slightly smaller than the inner diameter D2 of the body of an insertion tube (*e.g.,* diameter D2 of the insertion tube 1000 depicted in FIGS. 5A and 5B). The radiused surface 612 of the cylindrical body 602 is designed to push against the distal end of a stopper to provide straightness and stability during the insertion of the stopper into the syringe barrel. The cylindrical body 602 has a diameter D4 that may range from about 2 mm to about 18 mm, including any and all subranges therebetween. In other embodiments, the radiused surface 612 may include or be formed of shapes other than a radius, such as, for example, a flat section, a straight taper (*e.g.* linear), curvilinear, rounded, or have multiple tapers. In at least one other embodiment, a stopper without an internal cavity may be used and the insertion pin may be modified to reduce or even eliminate the pin tip end, such as is depicted in FIG. 6C. As shown in FIG. 6C, the insertion pin 605 is devoid of a pin tip end and instead is formed of a flat or substantially flat surface 614.

[0078] Turning back to FIGS. 6A and FIG 6B, the pin tip end 610 has a length (L) that may be approximately the depth of the inner cavity of a stopper. In some embodiments, the pin tip end 610 has a length from about 3 mm to about 8 mm, from about 4 mm to about 7 mm, from about 4.5 mm to 5.5 mm, or from about 5 mm to about

6 mm. In addition, the pin tip end 610 may have a width (W) that may be approximately the width of the inner cavity of a stopper. In some embodiments, the pin tip end 610 has a width from about 0.5 mm to about 5 mm, from about 1 mm to about 4 mm, from about 1 mm to about 3 mm, from about 2 mm to about 3 mm, from about 1.5 mm to about 2.5 mm, from about 3 mm to about 6 mm, from about 5 mm to about 9 mm, or from 8 mm to about 11 mm. The combination of the width (W) and length (L) of the pin tip end 610 creates a volume that is compatible with the cavity of the stopper during insertion. In the embodiment in FIGS. 6A and 6B, the tip end 610 has a rounded end. The stopper 40 may be inserted into the insertion tube 1000 at a peak insertion force that ranges from about 10 N to about 200 N, from about 20 N to about 100 N, from about 30 N to about 80 N, from about 40 N to about 60 N, or from about 40 N to about 60 N. In some embodiments, the peak insertion force is greater than zero but less than about 50 N, greater than zero but less than about 40 N, greater than zero but less than about 30 N, or greater than zero but less than about 20 N.

[0079] The insertion pins 600 and 605 may be formed from a polymeric material such as polyether ether ketone (PEEK), polytetrafluoroethylene (PTFE), expanded polytetrafluoroethylene (ePTFE), or metallic materials such as stainless steel or a combination thereof.

[0080] Turning now to FIGS. 7A-7E and FIGS. 8A-8E, a cross section of a method for the insertion of a non-lubricated stopper at least partially covered with a polymer or expanded polymer layer or laminate layer into a non-lubricated syringe barrel (FIGS. 7A-7E) or into a non-lubricated cartridge tube (FIGS. 8A-8E) is depicted in a series of steps. It is to be noted that the tip cap 27 for the barrel 20 is shown in FIGS. 7A-7E for illustrative purposes only. In FIGS. 7A-7E and FIGS. 8A-8E, an insertion rod 650 is shown that includes both an insertion pin 600 (FIGS. 7A-7E) or an insertion pin 605 (FIGS. 8A-8E) and a machine adapter 620 Initially, as shown in FIG. 7A, a stopper 40 having a cavity 48 is placed into the placement region 1042 located at the proximal end 1012 of the insertion tube 1000. The distal end of the insertion tube 1000 is indicated generally by reference numeral 1014. The insertion tube 1000 is positioned above and aligned with the inner surface 25 of the syringe barrel 20. In some embodiments, the syringe barrel 20 has already been filled with a therapeutic solution 55. In FIG. 8A, a

solid stopper 40 (*i.e.*, without a cavity therein) is placed into the placement region 1042 located at the proximal end 1012 of the insertion tube 1000. The distal end of the insertion tube 1000 is indicated generally by reference numeral 1014. The insertion tube 1000 is positioned above and aligned with the inner surface 25 of the cartridge tube 32. In some embodiments, the cartridge tube 32 has already been filled with a therapeutic solution 55. Looking at FIG. 7B and FIG. 8B, the body 1010 of the insertion tube 1000 is then moved down into the inner space of the syringe barrel 20 or cartridge tube 32, respectively, in the direction of arrow A1 without contacting the inner surface 25 of the syringe barrel 20 (FIG. 7B) or cartridge tube 32 (FIG. 8B). It is to be appreciated that a gap is located between the insertion tube 1000 and the inner surface 25 of the barrel 20 or cartridge tube 32 to allow for pressure venting. In addition, the steps depicted and described in FIGS. 7A and 7B and FIGS. 8A and 8B may happen either sequentially, as described above, or simultaneously.

[0081] The body 1010 of the insertion tube 1000 is moved until it is past the barrel flange 70 (FIG. B) or end portion 36 of cartridge tube 32 (FIG. 8B) and is stopped when the distal opening 1050 of the insertion tube 1000 is located at a specific location that will determine the final position of the stopper 40 in relation to the surface of the liquid therapeutic solution 55. As shown in FIG. 7C and 8C, the insertion rod 650 is then used to translate the stopper 40 through the length of the insertion tube 1000 in the direction of arrow A2, moving through the transition region 1040 until it reaches the distal opening 1050 of the insertion tube 1000. It is to be appreciated that the location of the sealing ribs of the stopper 40 inside the insertion tube 1000 should be properly placed when the stopper 40 is positioned at the distal opening 1050. For example, if the stopper 40 is positioned too far from the distal opening 1050 of the insertion tube 1000, the stopper 40 may be incorrectly placed into the barrel 20 (FIG. 7C) or cartridge tube 32 (FIG. 8C) when the insertion tube 1000 is retracted. Alternatively, if the stopper 40 is over inserted through the insertion tube 1000 such that one or more of the sealing ribs protrudes from the distal opening 1050 of the insertion tube 1000, then the head space H2 above the therapeutic solution 55 may be pressurized during the insertion process. Turning to FIGS. 7D and 8D, the insertion rod 650 holds the stopper 40 in position while the insertion tube 1000 is retracted in the direction of arrow A3 until the stopper 40 has

exited the distal opening 1050 of the insertion tube 1000. As a result, the stopper 40 is now positioned in the barrel 20 (FIG. 7D) or cartridge tube 32 (FIG. 8D) creating the desired final headspace H2. In FIG. 7E and FIG. 8E, the insertion rod 650 and insertion tube 1000 are fully retracted from the barrel 20 (FIG. 7E) or cartridge tube 32 (FIG. 8E) and stopper 40 in the direction of arrow A4. It is to be appreciated that the entire method of inserting a lubricant free stopper into a syringe barrel or cartridge tube is conducted without lubricants (such as, but not limited to, silicone or silicone oil), including the installation equipment (e.g., the insertion pin, the insertion tube, etc.).

[0082] An example of system 800 for assembling pre-filled syringe or cartridge is depicted in FIG. 9. The system includes a stopper feeder 810, for providing silicone free stoppers and a therapeutic feeder 850 for providing an active therapeutic of interest for a pre-filled syringe or cartridge. The system also includes an insertion tube 801 that has a placement region 820 and a body 840 having a diameter smaller than the placement region 820, and a transition zone 830 having an angle between 1 degree and 20 degrees that reduces the insertion diameter of the silicone free stoppers from the placement diameter 820 to the diameter of the body 840. The system also includes at least one syringe barrel or cartridge tube 870 (or alternatively an array of syringe barrels or cartridge tubes) positioned to receive the insertion tube 801. The system also includes an insertion rod 860 that provides for maneuvering the stopper in the insertion tube 801, where the maneuvering step is step D. The system further includes mechanisms to lower the insertion tube 801 into the syringe barrel 870, in a process step B, or remove the insertion tube 801 from the syringe barrel 870, in a process step E. In Step C the lubricant free stopper is placed in the placement region 820.

[0083] In one embodiment, an active therapeutic is fed to the silicone free syringe barrel or cartridge tube in step A. Sequentially, or at the same time, the stopper (not shown) is removed from the stopper feeder 801 and positioned in the placement region 820 in step C. The insertion tube 801 is lowered into the syringe barrel or cartridge tube 870 in step B. The stopper is then maneuvered down to the distal end of body 840 in step D but does not yet leave the insertion tube 801. In the next step, step E, the insertion rod 860 holds the stopper in a fixed position while the insertion tube is retracted within the barrel or cartridge tube a distance great enough to deploy the

stopper within the barrel or cartridge tube. Finally, in step F, the insertion rod 860 and insertion tube 801 is backed away from the stopper. It is to be noted that the insertion rod 860 and insertion tube 801 can removed from the barrel or cartridge tube 870 sequentially or simultaneously.

[0084] In some embodiments, the insertion of the stopper into the syringe barrel 20 or cartridge tube 32 is considered to be successful if there are less than 10 lines formed (*e.g.*, grooved or etched) on the front sealing rib 42 of the stopper 40 after insertion of the stopper 40 into one or more of the syringe barrel 20, the cartridge tube 32, or insertion tube 1000. The front sealing rib is the rib closest to the point of the stopper. The lines are visible with the use of 100x magnification on an optical microscope (*e.g.*, Keyence VHX-5000). In some embodiments, the front sealing rib of the stopper may have from 1 line to 20 lines, from 1 line to 15 lines, from 5 lines to 10 lines, from 1 line to 5 lines, or from 1 line to 3 lines. In exemplary embodiments, the stopper does not have greater than 30 lines, as this is associated with a high probability of syringe failure. In some embodiments, there may be no lines present on the front sealing rib of the stopper. Although not depicted pictorially, this "line count" method equally applies to determining the quality of an insertion tube, syringe barrel, or other component through which the stopper is moved to its final placement (*i.e.*, the insertion point). In some embodiments, the internal surface of the body of the insertion tube creates less than 30 lines (*e.g.*, 1 to 30 lines) as measured on any rib in contact with the barrel or cartridge, such as, for example, the front sealing rib of the stopper. When there are less than 30 lines, there is less potential for the stopper seal to fail. Advantageously, there would be less than or equal to 25 lines (*e.g.*, 1 to 25 lines), less than or equal to 20 lines (*e.g.*, 1 to 20 lines), less than or equal to 15 lines (*e.g.*, 1 to 15 lines), less than or equal to 10 lines (*e.g.*, 1 to 10 lines), less than or equal to 5 lines (*e.g.*, 1 to 5 lines), or less than or equal to 3 lines (*e.g.*, 1 to 3 lines).

[0085] In addition, the insertion of the stopper into the barrel or cartridge tube is considered to be successful if the helium leak rate of the stoppered syringe or cartridge is less than 1×10^{-8} sccs or less than 1×10^{-7} sccs. In some embodiments, the helium leak rate is not greater than 6×10^{-6} sccs. The helium leak rate may be determined according to the method set forth in U.S. Patent No. 10,471,211 to Rusch, *et al.* A

description of the helium leak rate and results of the same are described in Example 1 below. It is to be appreciated that the helium leak rate may be used in the same manner as the "line count" method (described above) to determine the quality of an insertion tube, syringe barrel, cartridge tube, or other component through which the stopper is moved to its insertion point.

[0086] In some embodiments, successful insertion (as defined by helium leak rate and/or line counts) of the lubricant free stopper in a lubricant free syringe barrel or lubricant free cartridge tube can be achieved by modifying the average surface roughness (S_a) of the insertion tube and/or the average kurtosis (S_{ku}) of the inside surface of the insertion tube. The target average surface roughness (S_a) and/or average kurtosis (S_{ku}) of the inside surface of the insertion tube can be achieved by a variety of methods known to one of ordinary skill in the art including, but not limited to, electropolishing, extrude honing, or a combination thereof. The test method for the average surface roughness (S_a) and average kurtosis (S_{ku}) and the results of the same are described in Example 1.

[0087] In some embodiments, the insertion tube may have an average surface roughness (S_a) from about 20 nm to about 400 nm, from about 20 nm to about 120 nm, from about 30 nm to about 80 nm, from about 30 nm to about 50 nm, from about 100 nm to about 300 nm, or from about 150 nm to about 250 nm. In some embodiments, the average surface roughness (S_a) is 25 nm or less. In addition, the insertion tube may have an average kurtosis (S_{ku}) from zero to less than about 3, from zero to less than about 4, from zero to less than about 5, from zero to less than about 6, from zero to less than about 7, or from zero to less than about 8. The insertion force combined with the average surface roughness (S_a) and/or average kurtosis (S_{ku}) define a space for the successful insertion of a stopper for each geometry of insertion tube.

[0088] At least the syringe barrel and stopper (*e.g.*, syringe components) or the cartridge tube and stopper (*e.g.* cartridge components), and vent tube, and insertion pin (*e.g.*, insertion components) are "lubricant free" or "substantially lubricant free." The term "lubricant free" as used herein is meant to denote that there are no lubricants of any kind, either intentionally or accidentally, added to the syringe barrel, cartridge tube, stopper, and/or to any equipment for manufacturing the same. Any amount of lubricant

that may be present is only present in a trace amount (*i.e.*, undetectable by any known measuring equipment or method). In some embodiments, however, lubricants may be inadvertently added through improper handling or residual lubricant on the manufacturing equipment; however, such lubricants may be present, so long as they are not intentionally added and are present in only a trace amount. It is to be appreciated that the needle of a syringe barrel purposefully has a lubricant thereon for ease of insertion into a patient. However, the needle is not considered to be within the purview of the present disclosure.

[0089] The term "substantially lubricant free" is meant to denote that there may be an amount of lubricant present that is detectable by any known measuring equipment or method. In some embodiments, this means that there may be from about 0 µg to about 5 µg, from about 1 µg to about 5 µg, or from about 2 µg to about 5 µg of lubricant present on the inner surface of the syringe. The absence or substantial absence of lubricants can be measured using gas chromatography (GC) mass spectrometry or inductively coupled plasma (ICP) mass spectrometry. Substantially lubricant free may also or alternatively be measured by the amount of particles in the syringe barrel that are measured in water for injection (WFI) after the WFI has been exposed to a fully assembled syringe (*e.g.*, a glass barrel and stopper and alternatively at least one therapeutic compound). In some embodiments, the amount of particles in the barrel may be less than about 600 particles / mL for particles greater than 10 µm in size or less than 60 particles /mL for particles greater than 25 µm in size when measured in WFI.

[0090] In some embodiments, lubricants other than silicone-based lubricants may be permitted. Common silicone-based lubricants include silicone oil or silicone grease, siloxanes, polysiloxane, organosiloxane, polyorganosiloxane, silicate esters, and similar compounds and combination thereof. In other embodiments, water based lubricants (e.g., polyethylene glycol, glycerin, cellulose ether), oil based lubricants (e.g., as petroleum jelly, paraffins, and olefins), and combinations thereof may be present on the inner surface of the syringe barrel or cartridge tube. In further embodiments, there may be no lubricant of any kind present on the inner surface of the syringe barrel or cartridge tube, but there may be a finish or a polish on the syringe barrel or cartridge tube.

[0091] It is to be appreciated that the ranges described herein may be utilized in conjunction with a 0.5 mL to a 20 mL syringe or cartridge, but may be appropriately scaled to smaller or larger syringes or cartridges. It should also be understood that one or more design features of the syringes described herein can be combined with other features of other syringes and cartridges described herein.

[0092] In another aspect, the syringe barrel, the cartridge tube, the plunger rod, and the stopper described herein may be used in combination with different therapeutic compounds such as, for example, drugs and biologics, including but not limited to, antibodies, antisense, RNA interference, gene therapy, primary and embryonic stem cells, vaccines, and combinations thereof. For instance, the embodiments described herein may be utilized in combination with any or all of the following biologics and/or therapeutic compounds.

[0093] Cell therapy using cells that are derived primarily from endoderm such as Exocrine secretory epithelial cells and Hormone-secreting cells; ectoderm such as Keratinizing epithelial cells, Wet stratified barrier epithelial cells, Sensory transducer cells, Autonomic neuron cells, Sense organ and peripheral neuron supporting cells, Central nervous system neurons and glial cells, Lens cells; mesoderm such as Metabolism and storage cells, Barrier function cells (lung, gut, exocrine glands, and urogenital tract), Extracellular matrix cells, Contractile cells, Blood and immune system cells, Germ cells, Nurse cell, Interstitial cells or a combination thereof. Additionally cells that are genetically, chemically or physically altered or modified are considered to be in the scope of the disclosure.

[0094] Examples of Exocrine secretory epithelial cells include, but are not limited to, Salivary gland mucous cell, Salivary gland number 1, Von Ebner's gland cell in tongue, Mammary gland cell, Lacrimal gland cell, Ceruminous gland cell in ear, Eccrine sweat gland dark cell, Eccrine sweat gland clear cell, Apocrine sweat gland cell, Gland of Moll cell in eyelid, Sebaceous gland cell, Bowman's gland cell in nose, Brunner's gland cell in duodenum, Seminal vesicle cell, Prostate gland cell, Bulbourethral gland cell, Bartholin's gland cell, Gland of Littre cell, Uterus endometrium cell, Isolated goblet cell of respiratory and digestive tracts, Stomach lining mucous cell, Gastric gland zymogenic cell, Gastric gland oxyntic cell, Pancreatic acinar cell, Paneth cell of small intestine,

Type II pneumocyte of lung, Clara cell of lung; Hormone-secreting cells including but not limited to: Anterior pituitary cells, Intermediate pituitary cell, Magnocellular neurosecretory cells, Gut and respiratory tract cells, Thyroid gland cells, Parathyroid gland cells, Adrenal gland cells, Leydig cell of testes secreting testosterone, Theca internal cell of ovarian follicle secreting estrogen, Corpus luteum cell of ruptured ovarian follicle secreting progesterone, Juxtaglomerular cell, Macula densa cell of kidney, Peripolar cell of kidney, Mesangial cell of kidney, Pancreatic islets; Keratinizing epithelial cells including but not limited to: Epidermal keratinocyte, Epidermal basal cell, Keratinocyte of fingernails and toenails, Nail bed basal cell, Medullary hair shaft cell, Cortical hair shaft cell, Cuticular hair shaft cell, Cuticular hair root sheath cell, Hair root sheath cell of Huxley's layer, Hair root sheath cell of Henle's layer, External hair root sheath cell, Hair matrix cell; Wet stratified barrier epithelial cells including but not limited to: Surface epithelial cell of stratified squamous epithelium and basal cell of epithelia of cornea, tongue, oral cavity, esophagus, anal canal, distal urethra and vagina, Urinary epithelium cell; Sensory transducer cells including but not limited to: Auditory inner hair cell of organ of Corti, Auditory outer hair cell of organ of Corti, Basal cell of olfactory epithelium, Cold-sensitive primary sensory neurons, Heat-sensitive primary sensory neurons, Merkel cell of epidermis, Olfactory receptor neuron, Pain-sensitive primary sensory neurons, Photoreceptor cells of retina in eye: Proprioceptive primary sensory neurons, Touch-sensitive primary sensory neurons, Type I carotid body cell, Type II carotid body cell, Type I hair cell of vestibular system of ear, Type II hair cell of vestibular system of ear, Type I taste bud cell; Autonomic neuron cells including but not limited to: Cholinergic neural cell, Adrenergic neural cell, Peptidergic neural cell; Sense organ and peripheral neuron supporting cells including but not limited to: Inner pillar cell of organ of Corti, Outer pillar cell of organ of Corti, Inner phalangeal cell of organ of Corti, Outer phalangeal cell of organ of Corti, Border cell of organ of Corti, Hensen cell of organ of Corti, Vestibular apparatus supporting cell, Taste bud supporting cell, Olfactory epithelium supporting cell, Schwann cell, Satellite glial cell, Enteric glial cell; Central nervous system neurons and glial cells including but not limited to: Astrocyte, Neuron cells, Oligodendrocyte, Spindle neuron; Lens cells including but not limited to: Anterior lens epithelial cell, Crystallin-containing lens fiber cell; Metabolism and storage

cells including but not limited to: Adipocytes: Liver lipocyte; Barrier function cells including but not limited to: Kidney parietal cell, Kidney glomerulus podocyte, Kidney proximal tubule brush border cell, Loop of Henle thin segment cell, Kidney distal tubule cell, Kidney collecting duct cell, Principal cells, Intercalated cells, Type I pneumocyte, Pancreatic duct cell, Nonstriated duct cell, Principal cell, Intercalated cell, Duct cell, Intestinal brush border cell, Exocrine gland striated duct cell, Gall bladder epithelial cell, Ductulus efferens nonciliated cell, Epididymal principal cell, Epididymal basal cell; Extracellular matrix cells including but not limited to: Ameloblast epithelial cell, Planum semilunatum epithelial cell of vestibular system of ear, Organ of Corti interdental epithelial cell, Loose connective tissue fibroblasts, Corneal fibroblasts, Tendon fibroblasts, Bone marrow reticular tissue fibroblasts, Other nonepithelial fibroblasts, Pericyte, Nucleus pulposus cell of intervertebral disc, Cementoblast/cementocyte, Odontoblast/odontocyte, Hyaline cartilage chondrocyte, Fibrocartilage chondrocyte, Elastic cartilage chondrocyte, Osteoblast/osteocyte, Osteoprogenitor cell, Hyalocyte of vitreous body of eye, Stellate cell of perilymphatic space of ear, Hepatic stellate cell, Pancreatic stelle cell; Contractile cells including but not limited to: Skeletal muscle cell, Satellite cell, Heart muscle cells, Smooth muscle cell, Myoepithelial cell of iris, Myoepithelial cell of exocrine glands; Blood and immune system cells including but not limited to: Erythrocyte, Megakaryocyte, Monocyte, Connective tissue macrophage, Epidermal Langerhans cell, Osteoclast, Dendritic cell, Microglial cell, Neutrophil granulocyte, Eosinophil granulocyte, Basophil granulocyte, Hybridoma cell, Mast cell, Helper T cell, Suppressor T cell, Cytotoxic T cell, Natural Killer T cell, B cell, Natural killer cell, Reticulocyte, Stem cells and committed progenitors for the blood and immune system; Germ cells including but not limited to: Oogonium/Oocyte, Spermatid, Spermatocyte, Spermatogonium cell, Spermatozoon; Nurse cell including but not limited to: Ovarian follicle cell, Sertoli cell, Thymus epithelial cell; Interstitial cells including but not limited to: Interstitial kidney cells and a combination thereof.

[0095] Examples of antibodies, antisense, RNA interference, or gene therapy made to protein targets or gene(s) of: Ataxia Telangiectasia Mutated, Tumor Protein p53, Checkpoint kinase 2, breast cancer susceptibility protein, Double-strand break repair protein, DNA repair protein RAD50, Nibrin, p53-binding protein, Mediator of DNA

damage checkpoint protein, H2A histone family member X, Microcephalin, C-terminal-binding protein 1, Structural maintenance of chromosomes protein 1A; Esterases; Phosphatases; Examples of Ion channels include but are not limited to: ligand-gated ion channels, voltage-gated ion channels; Examples of growth factors include but are not limited to: nerve growth factor (NGF), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), C-fos-induced growth factor (FIGF), platelet-activating factor (PAF), transforming growth factor beta (TGF-β), b, one morphogenetic proteins (BMPs), Activin, inhibin, fibroblast growth factors (FGFs), granulocyte-colony stimulating factor (G-CSF), granulocyte-macrophage colony stimulating factor (GM-CSF), glial cell line-derived neurotrophic factor (GDNF), growth differentiation factor-9 (GDF9), epidermal growth factor (EGF), transforming growth factor-α (TGF- α), growth factor (KGF), migration-stimulating factor (MSF), hepatocyte growth factor-like protein (HGFLP), hepatocyte growth factor (HGF), hepatoma-derived growth factor (HDGF), Insulin-like growth factors; Examples of G Protein–Coupled Receptors (GPCR) include but are not limited to: Adenosine receptor family, Adrenergic receptor family, Angiotensin II receptor, Apelin receptor, Vasopressin receptor family, Brain-specific angiogenesis inhibitor family, Bradykinin receptor family, Bombesin receptor family, Complement component 3a receptor 1, Complement component 5a receptor 1, Calcitonin receptor family, Calcitonin receptor-like family, Calcium-sensing receptor, Cholecystokinin A receptor (CCK1), Cholecystokinin B receptor (CCK2), Chemokine (C-C motif) receptor family, Sphingosine 1-phosphate receptor family, Succinic receptor, Cholinergic receptor family. Chemokine-like receptor family, Cannabinoid receptor family, Corticotropin releasing hormone receptor family, prostaglandin D2 receptor, Chemokine C-X3-C receptor family, Chemokine (C-X-C motif) receptor family, Burkitt lymphoma receptor, Chemokine (C-X-C motif) receptor family, Cysteinyl leukotriene receptor 2 (CYSLT2), chemokine receptor (FY), Dopamine receptor family, G protein-coupled receptor 183 (GPR183), Lysophosphatidic acid receptor family, Endothelin receptor family, Coagulation factor II (thrombin) receptor family, Free fatty acid receptor family, Formylpeptide receptor family, Follicle stimulating hormone receptor (FSHR), gamma-aminobutyric acid (GABA) B receptor, Galanin receptor family, Glucagon receptor, Growth hormone releasing hormone receptor (GHRH), Ghrelin receptor

(ghrelin), Growth hormone secretagogue receptor 1b (GHSR1b), Gastric inhibitory polypeptide receptor (GIP), Glucagon-like peptide receptor family, Gonadotropin-releasing hormone receptor (GnRH), pyroglutamylated RFamide peptide receptor (QRFPR), G protein-coupled bile acid receptor 1 (GPBA), Hydroxycarboxylic acid receptor family, Lysophosphatidic acid receptor 4 (LPA4) Lysophosphatidic acid receptor 5 (GPR92), G protein-coupled receptor 79 pseudogene (GPR79), Hydroxycarboxylic acid receptor 1 (HCA1), G-protein coupled receptor (C5L2, FFA4, FFA4, FFA4, GPER, GPR1, GPR101, GPR107, GPR119, GPR12, GPR123, GPR132, GPR135, GPR139, GPR141, GPR142, GPR143, GPR146, GPR148, GPR149, GPR15, GPR150, GPR151, GPR152, GPR157, GPR161, GPR162, GPR17, GPR171, GPR173, GPR176, GPR18, GPR182, GPR20, GPR22, GPR25, GPR26, GPR27, GPR3, GPR31, GPR32, GPR35, GPR37L1, GPR39, GPR4, GPR45, GPR50, GPR52, GPR55, GPR6, GPR61, GPR65, GPR75, GPR78, GPR83, GPR84, GPR85, GPR88, GPR97, TM7SF1), Metabotropic glutamate receptor family, Gastrin releasing peptide receptor (BB2), Orexin receptor family, Histamine receptor family, 5-hydroxytryptamine receptor family, KISS1-derived peptide receptor (kisspeptin), Leucine-rich repeat-containing G protein-coupled receptor family, horiogonadotropin receptor (LH), Leukotriene B4 receptor (BLT1), Adenylate Cyclase Activating Polypeptide 1 Receptor 1 (mPAC1), Motilin receptor, Melanocortin receptor family, Melanin concentrating hormone receptor 1 (MCH1), Neuropeptide Y1 receptor (Y1), Neuropeptide Y2 receptor (NPY2R), Opioid receptor family, Oxytocin recepter (OT), P2Y Purinoceptor 12 (mP2Y12), P2Y Purinoceptor 6 (P2Y6), Pancreatic polypeptide receptor family, Platelet-activating factor receptor family, Prostaglandin E receptor family, Prostanoid IP1 receptor (IP1), MAS-related GPR, member family, Rhodopsin (Rhodopsin), Relaxin family peptide receptor family, Somatostatin receptor family, Tachykinin receptor family, Melatonin receptor family, Urotensin receptor family, Vasoactive intestinal peptide receptor 1 (mVPAC1), Neuromedin B Receptor (BB1), Neuromedin U receptor 1 (NMU1), Neuropeptides B/W receptor family, Neuropeptide FF receptor 1 (NPFF1), neuropeptide S receptor 1 (NPS receptor), Neuropeptide Y receptor family, Neurotensin receptor 1 (NTS1), Opsin 5 (OPN5), Opioid receptor-like receptor (NOP), Oxoeicosanoid (OXE) receptor 1 (OXE), Oxoglutarate (alpha-ketoglutarate) receptor 1 (OXGR1), Purinergic receptor family,

Pyrimidinergic receptor family, Prolactin releasing hormone receptor (PRRP), Prokineticin receptor family, Platelet activating receptor (PAF), Prostaglandin F receptor family, Prostaglandin I2 (prostacyclin) receptor family, Parathyroid hormone receptor family, muscarinic 4 (rM4), Prostanoid DP2 receptor (rGPR44), Prokineticin receptor family, Relaxin family peptide receptor family, Secretin receptor (secretin), Smoothened, Frizzled class receptor (Smoothened), trace amine associated receptor family, Tachykinin family, Thromboxane A2 receptor (TP), Thyrotropin-releasing hormone receptor (TRH1), Thyroid Stimulating Hormone Receptor (TSH); Examples of Protein kinases include but are not limited to: AP2 associated kinase, Homo sapiens ABL proto-oncogene 1 - non-receptor tyrosine-protein kinase family, c-abl oncogene 1 receptor tyrosine kinase family, v-abl Abelson murine leukemia viral oncogene homolog 2, activin A receptor family, chaperone - ABC1 activity of bc1 complex homolog (S. pombe) (ADCK3), aarF domain containing kinase 4 (ADCK4), v-akt murine thymoma viral oncogene homolog family, anaplastic lymphoma receptor tyrosine kinase family, protein kinase A family, protein kinase B family, ankyrin repeat and kinase domain containing 1 (ANKK1), NUAK family - SNF1-like kinase, mitogen-activated protein kinase family aurora kinase A (AURKA), aurora kinase B (AURKB), aurora kinase C (AURKC), AXL receptor tyrosine kinase (AXL), BMP2 inducible kinase (BIKE), B lymphoid tyrosine kinase (BLK), bone morphogenetic protein receptor family, BMX non-receptor tyrosine kinase (BMX), v-raf murine sarcoma viral oncogene homolog B1 (BRAF), protein tyrosine kinase 6 (BRK), BR serine/threonine kinase family, Bruton agammaglobulinemia tyrosine kinase (BTK), calcium/calmodulin-dependent protein kinase family, cyclin-dependent kinase family, cyclin-dependent kinase-like family, CHK1 checkpoint homolog (S. pombe) (CHEK1), CHK2 checkpoint homolog (S. pombe) (CHEK2), Insulin receptor, isoform A (INSR), Insulin receptor, isoform B (INSR), rho-interacting serine/threonine kinase (CIT), v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (KIT), CDC-Like Kinase family - Hepatocyte growth factor receptor (MET), Proto-oncogene tyrosine-protein kinase receptor, colony-stimulating factor family receptor, c-src tyrosine kinase (CSK), casein kinase family, megakaryocyte-associated tyrosine kinase (CTK), death-associated protein kinase family, doublecortin-like kinase family, discoidin domain receptor tyrosine kinase, dystrophia myotonica-protein kinase

(DMPK), dual-specificity tyrosine-(Y)-phosphorylation regulated kinase family, epidermal growth factor receptor family, eukaryotic translation initiation factor 2-alpha kinase 1 (EIF2AK1), EPH receptor family, Ephrin type-A receptor family, Ephrin type-B receptor family, v-erb-b2 erythroblastic leukemia viral oncogene homolog family, mitogen-activated protein kinase family, endoplasmic reticulum to nucleus signaling 1 (ERN1), PTK2 protein tyrosine kinase 2 (FAK), fer (fps/fes related) tyrosine kinase (FER). feline sarcoma oncogene (FES), Fibroblast growth factor receptor family, Gardner-Rasheed feline sarcoma viral (v-fgr) oncogene homolog (FGR), fms-related tyrosine kinase family, Fms-related tyrosine kinase family, fyn-related kinase (FRK), FYN oncogene related to SRC, cyclin G associated kinase (GAK), eukaryotic translation initiation factor 2 alpha kinase, Growth hormone receptor. G protein-coupled receptor kinase 1 (GRK1), G protein-coupled receptor kinase family, glycogen synthase kinase family, germ cell associated 2 (haspin) (HASPIN), Hemopoietic cell kinase (HCK), homeodomain interacting protein kinase family, mitogen-activated protein kinase family, hormonally up-regulated Neu-associated kinase (HUNK), intestinal cell (MAK-like) kinase (ICK), Insulin-like growth factor 1 receptor (IGF1R), conserved helix-loop-helix ubiquitous kinase (IKK-alpha), inhibitor of kappa light polypeptide gene enhancer in B-cells - kinase beta family, insulin receptor (INSR), insulin receptor-related receptor (INSRR), interleukin-1 receptor-associated kinase family, IL2-inducible T-cell kinase (ITK), Janus kinase family, Kinase Insert Domain Receptor, v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog, lymphocyte-specific protein tyrosine kinase (LCK), LIM domain kinase family, serine/threonine kinase family leucine-rich repeat kinase family, v-yes-1 Yamaguchi sarcoma viral related oncogene homolog (LYN), male germ cell-associated kinase (MAK),, MAP/microtubule affinity-regulating kinase family, microtubule associated serine/threonine kinase family, maternal embryonic leucine zipper kinase, c-mer proto-oncogene tyrosine kinase (MERTK), met proto-oncogene (hepatocyte growth factor receptor), MAP kinase interacting serine/threonine kinase family, myosin light chain kinase family, mixed lineage kinase domain-like protein isoform, CDC42 binding protein kinase family, serine/threonine kinase family, macrophage stimulating 1 receptor (c-met-related tyrosine kinase) (MST1R), mechanistic target of rapamycin (serine/threonine kinase) (MTOR), muscle- skeletal- receptor tyrosine kinase (MUSK),

myosin light chain kinase family, NIMA (never in mitosis gene a)-related kinase family, serine/threonine-protein kinase NIM1 (NIM1), nemo-like kinase (NLK), oxidative-stress responsive 1 (OSR1), p21 protein (Cdc42/Rac)-activated kinase family, PAS domain containing serine/threonine kinase, Platelet-derived growth factor receptor family, 3-phosphoinositide dependent protein kinase-1 (PDPK1), Calcium-dependent protein kinase 1, phosphorylase kinase gamma family, Phosphatidylinositol 4,5-bisphosphate 3-kinase, phosphoinositide-3-kinase family, phosphatidylinositol 4-kinase family. phosphoinositide kinase, FYVE finger containing, Pim-1 oncogene (PIM1), pim-2 oncogene (PIM2), pim-3 oncogene (PIM3), phosphatidylinositol-4-phosphate 5-kinase family, phosphatidylinositol-5-phosphate 4-kinase family protein kinase, membrane associated tyrosine/threonine 1 (PKMYT1), protein kinase N family, polo-like kinase family, protein kinase C family, protein kinase D family, cGMP-dependent protein kinase family, eukaryotic translation initiation factor 2-alpha kinase 2 (PRKR), X-linked protein kinase (PRKX), Prolactin receptor (PRLR), PRP4 pre-mRNA processing factor 4 homolog B (yeast) (PRP4), PTK2B protein tyrosine kinase 2 beta (PTK2B), SIK family kinase 3 (QSK), v-raf-1 murine leukemia viral oncogene homolog 1 (RAF1), Neurotrophic tyrosine kinase receptor type family, receptor (TNFRSF)-interacting serine-threonine kinase family, dual serine/threonine and tyrosine protein kinase (RIPK5), Rho-associated, coiled-coil containing protein kinase family, c-ros oncogene 1, receptor tyrosine kinase (ROS1), ribosomal protein S6 kinase family, SH3-binding domain kinase 1 (SBK1), serum/glucocorticoid regulated kinase family, Putative uncharacterized serine/threonine-protein kinase (Sugen kinase 110) (SgK110), salt-inducible kinase family, SNF related kinase (SNRK), src-related kinase , SFRS protein kinase family, , Spleen tyrosine kinase (SYK), TAO kinase family, TANK-binding kinase 1 (TBK1), tec protein tyrosine kinase (TEC), testis-specific kinase 1 (TESK1), transforming growth factor, beta receptor family, tyrosine kinase with immunoglobulin-like and EGF-like domains 1 (TIE1), TEK tyrosine kinase, endothelial (TIE2), Angiopoietin-1 receptor (Tie2), tousled-like kinase family, TRAF2 and NCK interacting kinase (TNIK), non-receptor tyrosine kinase family, TNNI3 interacting kinase (TNNI3K), transient receptor potential cation channel, testis-specific serine kinase family, TTK protein kinase (TTK), TXK tyrosine kinase (TXK), Tyrosine kinase 2 (TYK2), TYRO3

protein tyrosine kinase (TYRO3), unc-51-like kinase family, phosphatidylinositol 3-kinase, vaccinia related kinase 2 (VRK2), WEE1 homolog family, WNK lysine deficient protein kinase family, v-yes-1 Yamaguchi sarcoma viral oncogene homolog 1 (YES), sterile alpha motif and leucine zipper containing kinase AZK (ZAK), zeta-chain (TCR) associated protein kinase 70kDa (ZAP70); Examples of nuclear hormone receptors include but are not limited to: Androgen receptor (AR), Estrogen related receptor alpha (ESRRA), Estrogen receptor 1 (ESR1), Nuclear receptor subfamily 1 - group H - member 4 (NR1H4), Nuclear receptor subfamily 3 - group C - member 1 (glucocorticoid receptor) (NR3C1), Nuclear receptor subfamily 1 - group H - member 3 (Liver X receptor α) (NR1H3), Nuclear receptor subfamily 1 - group H - member 2 (Liver X receptor β) (NR1H2), Nuclear receptor subfamily 1 - group H - member 2 (Liver X receptor β) (NR1H2), Nuclear receptor subfamily 3 - group C - member 2 (Mineralcorticoid receptor) (NR3C2), Peroxisome Proliferator Activated Receptor alpha (PPARA), Peroxisome Proliferator Activated Receptor gamma (PPARG), Peroxisome Proliferator Activated Receptor delta (PPARD), Progesterone receptor α (PGR), Progesterone receptor β (PGR), Retinoic acid receptor - alpha (RARA), Retinoic acid receptor - beta (RARB), Retinoid X receptor - alpha (RXRA), Retinoid X receptor - gamma (RXRG), Thyroid hormone receptor - alpha (THRA), Thyroid hormone receptor - beta (THRB), Retinoic acid-related orphan receptor, Liver X receptor, Farnesoid X receptor, Vitamin D receptor, Pregnane X receptor, Constitutive androstane receptor, Hepatocyte nuclear factor 4, Oestrogen receptor, Oestrogen-related receptor, Glucocortioic receptor, Nerve growth factor-induced-B, Germ cell nuclear factor; Examples of Epigenetic targets include but are not limited to: ATPase family AAA domain-containing protein 2 (ATAD2A), ATPase family - AAA domain containing 2B (ATAD2B), ATPase family AAA domain containing - 2B (ATAD2B), bromodomain adjacent to zinc finger domain - 1A (BAZ1A), bromodomain adjacent to zinc finger domain - 1B (BAZ1B), bromodomain adjacent to zinc finger domain - 2A (BAZ2A), bromodomain adjacent to zinc finger domain - 2A (BAZ2A), bromodomain adjacent to zinc finger domain - 2B (BAZ2B), bromodomain-containing protein 1 (BRD1), Bromodomain containing protein 2 - 1st bromodomain (BRD2), Bromodomain containing protein 2 - 1st & 2nd bromodomains (BRD2), bromodomain-containing

protein 2 isoform 1 - bromodomain 2 (BRD2(2)), bromodomain-containing protein 3 - bromodomain 1 (BRD3(1)), Bromodomain-containing protein 3 - 1st bromodomain (BRD3), Bromodomain-containing protein 3 - 1st & 2nd bromodomains (BRD3), bromodomain-containing protein 3 - bromodomain 2 (BRD3(2)), Bromodomain containing protein 4 - 1st bromodomain (BRD4), bromodomain-containing protein 4 isoform long - bromodomains 1 and 2 (BRD4(1 -2)), bromodomain-containing protein 4 isoform long - bromodomain 2 (BRD4(2)), bromodomain-containing protein 4 isoform short (BRD4(full-length -short-iso.)), Bromodomain containing protein 7 (BRD7), bromodomain containing 8 - bromodomain 1 (BRD8(1)), bromodomain containing 8 - bromodomain 2 (BRD8(2)), bromodomain-containing protein 9 isoform 1 (BRD9), Bromodomain containing testis-specific - 1st bromodomain (BRDT), Bromodomain containing testis-specific - 1st & 2nd bromodomains (BRDT), bromodomain testis-specific protein isoform b - bromodomain 2 (BRDT(2)), bromodomain and PHD finger containing - 1 (BRPF1), bromodomain and PHD finger containing - 3 (BRPF3), bromodomain and PHD finger containing - 3 (BRPF3), Bromodomain and WD repeat-containing 3 - 2nd bromodomain (BRWD3(2)), Cat eye syndrome critical region protein 2 (CECR2), CREB binding protein (CREBBP), E1A binding protein p300 (EP300), EP300 (EP300), nucleosome-remodeling factor subunit BPTF isoform 1 (FALZ), Nucleosome-remodeling factor subunit BPT (FALZ), Euchromatic histone-lysine N-methyltransferase 2 (EHMT2), Histone Acetyltransferase - KAT2A (GCN5L2), Euchromatic histone-lysine N-methyltransferase 1 (EHMT1), Histone-lysine N-methyltransferase MLL (MLL), Polybromo 1 - 1st bromodomain (PB1(1)), Polybromo 1 - 2nd bromodomain (PB1(2)), polybromo 1 - bromodomain 2 (PBRM1(2)), polybromo 1 - bromodomain 5 (PBRM1(5)), Histone acetyltransferase KAT2B (PCAF), PH-interacting protein - 1st bromodomain (PHIP(1)), PH-interacting protein - 2nd bromodomain (PHIP(2)), Protein kinase C-binding protein 1 (PRKCBP1), Protein arginine N-methyltransferase 3 (PRMT3), SWI/SNF related - matrix associated - actin dependent regulator of chromatin - subfamily a - member 2 (SMARCA2), SWI/SNF related - matrix associated - actin dependent regulator of chromatin - subfamily a - member 4 (SMARCA4), Nuclear body protein - SP110 (SP110), Nuclear body protein - SP140 (SP140), Transcription initiation factor TFIID subunit 1 (TAF1(1 -2)), TAF1 RNA

polymerase II - TATA box binding protein (TBP)-associated factor - 250kDa - bromodomain 2 (TAF1(2)), Transcription initiation factor TFIID subunit 1-like - 1st bromodomain (TAF1L(1)), Transcription initiation factor TFIID subunit 1-like - 2nd bromodomain (TAF1L(2)), tripartite motif containing 24 (TRIM24(Bromo.)), tripartite motif containing 24 (TRIM24(PHD -Bromo.)), E3 ubiquitin-protein ligase TRIM33 (TRIM33), tripartite motif containing 33 (TRIM33(PHD -Bromo.)), WD repeat 9 - 1st bromodomain (WDR9(1)), WD repeat 9 - 2nd bromodomain (WDR9(2)); membrane transport proteins including but not limited to ATP-binding cassette (ABC) superfamily, solute carrier (SLC) superfamily, multidrug resistance protein 1 (P-glycoprotein), organic anion transporter 1,and protein such as EAAT3, EAAC1, EAAT1, GLUT1, GLUT2, GLUT9, GLUT10, rBAT, AE1, NBC1, KNBC, CHED2, BTR1, NABC1, CDPD, SGLT1, SGLT2, NIS, CHT1, NET, DAT, GLYT2, CRTR, B0AT1, SIT1, XT3, y+LAT1, BAT1, NHERF1, NHE6, ASBT, DMT1, DCT1, NRAMP2, NKCC2, NCC, KCC3, NACT, MCT1, MCT8, MCT12, SLD, VGLUT3, THTR1, THTR2, PIT2, GLVR2, OCTN2, URAT1, NCKX1, NCKX5, CIC, PiC, ANT1, ORNT1, AGC1, ARALAR, Citrin, STLN2, aralar2, TPC, MUP1, MCPHA, CACT, GC1, PHC, DTD, CLD, DRA, PDS, Prestin, TAT1, FATP4, ENT3, ZnT2, ZnT10, AT1, NPT2A, NPT2B, HHRH, CST, CDG2F, UGAT, UGTL, UGALT, UGT1, UGT2, FUCT1, CDG2C, NST, PAT2, G6PT1, SPX4, ZIP4, LIV4, ZIP13, LZT-Hs9, FPN1, MTP1, IREG1, RHAG, AIM1, PCFT, FLVCR1, FLVCR2, RFT1, RFT2, RFT3, OATP1B1, OATP1B3, OATP2A1; structural proteins including but not limited to tubulin, heat shock protein, Microtubule-stabilizing proteins, Oncoprotein 18, stathmin, kinesin-8 and kinesin-14 family, Kip3, Kif18A; proteases including but not limited ADAM (a disintegrin and metalloprotease) family; Other molecule targets in signal transductions include but are not limited to: Cell division cycle 25 homolog A (CDC25A), forkhead box O3 (forkhead box O3), nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (NFKBIA), nuclear factor (erythroid-derived 2)-like 2 (NFE2L2), Natriuretic peptide receptor A (NPR1), Tumor necrosis factor receptor superfamily, member 11a (TNFRSF11A), v-rel reticuloendotheliosis viral oncogene homolog A (avian) (RELA), Sterol regulatory element binding transcription factor 2 (SREBF2), CREB regulated transcription coactivator 1 (CRTC1), CREB regulated transcription coactivator 2 (CRTC2), X-box

binding protein 1 (XBP1), Catenin (cadherin-associated protein), beta 1 (CTNNB1), and combinations thereof.

[0096] Examples of known biologics include, but are not limited to: Abbosynagis, Abegrin, Actemra, AFP-Cide, Antova, Arzerra, Aurexis, Avastin, Benlysta, Bexxar, Blontress, Bosatria, Campath, CEA-Cide, CEA-Scan, Cimzia, Cyramza, Ektomab, Erbitux, FibriScint, Gazyva, Herceptin, hPAM4-Cide, HumaSPECT, HuMax-CD4, HuMax-EGFr, Humira, HuZAF, Hybri-ceaker, Ilaris, Indimacis-125, Kadcyla, Lemtrada, LeukArrest, LeukoScan, Lucentis, Lymphomun, LymphoScan, LymphoStat-B, MabThera, Mycograb, Mylotarg, Myoscint, NeutroSpec, Numax, Nuvion, Omnitarg, Opdivo, Orthoclone OKT3, OvaRex, Panorex, Prolia, Prostascint, Raptiva, Remicade, Removab, Rencarex, ReoPro, Rexomun, Rituxan, RoActemra, Scintimun, Simponi, Simulect, Soliris, Stelara, Synagis, Tactress, Theracim, Theragyn, Theraloc, Tysabri, Vectibix, Verluma, Xolair, Yervoy, Zenapax, and Zevalin or combinations thereof.

[0097] Examples of known monoclonal antibodies include but are not limited to: 3F8, 8H9, Abagovomab, Abciximab, Abituzumab, Abrilumab, Actoxumab, Adalimumab, Adecatumumab, Aducanumab, Afasevikumab, Afelimomab, Afutuzumab, Alacizumab pegol, ALD518, ALD403, Alemtuzumab, Alirocumab, Altumomab pentetate, Amatuximab, AMG 334, Anatumomab mafenatox, Anetumab ravtansine, Anifrolumab, Anrukinzumab, Apolizumab, Arcitumomab, Ascrinvacumab, Aselizumab, Atezolizumab, Atinumab, Atlizumab, Atorolimumab, Avelumab, Bapineuzumab, Basiliximab, Bavituximab, Bectumomab, Begelomab, Belimumab, Benralizumab, Bertilimumab, Besilesomab, Bevacizumab, Bezlotoxumab, Biciromab, Bimagrumab, Bimekizumab, Bivatuzumab mertansine, Bleselumab, Blinatumomab, Blontuvetmab, Blosozumab, Bococizumab, Brazikumab, Brentuximab vedotin, Briakinumab, Brodalumab, Brolucizumab, Brontictuzumab, Burosumab, Cabiralizumab, Canakinumab, Cantuzumab mertansine, Cantuzumab ravtansine, Caplacizumab, Capromab pendetide, Carlumab, Carotuximab, Catumaxomab, cBR96-doxorubicin immunoconjugate, Cedelizumab, Cergutuzumab amunaleukin, Certolizumab pegol, Cetuximab, Citatuzumab bogatox, Cixutumumab, Clazakizumab, Clenoliximab, Clivatuzumab tetraxetan, Codrituzumab, Coltuximab ravtansine, Conatumumab, Concizumab, CR6261, Crenezumab, Crotedumab, Dacetuzumab, Daclizumab,

Dalotuzumab, Dapirolizumab pegol, Daratumumab, Dectrekumab, Demcizumab, Denintuzumab mafodotin, Denosumab, Depatuxizumab mafodotin, Derlotuximab biotin, Detumomab, Dinutuximab, Diridavumab, Domagrozumab, Dorlimomab aritox, Drozitumab, Duligotumab, Dupilumab, Durvalumab, Dusigitumab, Ecromeximab, Eculizumab, Edobacomab, Edrecolomab, Efalizumab, Efungumab, Eldelumab, Elgemtumab, Elotuzumab, Elsilimomab, Emactuzumab, Emibetuzumab, Emicizumab, Enavatuzumab, Enfortumab vedotin, Enlimomab pegol, Enoblituzumab, Enokizumab, Enoticumab, Ensituximab, Epitumomab cituxetan, Epratuzumab, Erenumab, Erlizumab, Ertumaxomab, Etaracizumab, Etrolizumab, Evinacumab, Evolocumab, Exbivirumab, Fanolesomab, Faralimomab, Farletuzumab, Fasinumab, FBTA05, Felvizumab, Fezakinumab, Fibatuzumab, Ficlatuzumab, Figitumumab, Firivumab, Flanvotumab, Fletikumab, Fontolizumab, Foralumab, Foravirumab, Fresolimumab, Fulranumab, Futuximab, Galcanezumab, Galiximab, Ganitumab, Gantenerumab, Gavilimomab, Gemtuzumab ozogamicin, Gevokizumab, Girentuximab, Glembatumumab vedotin, Golimumab, Gomiliximab, Guselkumab, Ibalizumab, Ibritumomab tiuxetan, Icrucumab, Idarucizumab, Igovomab, IMA-638, IMAB362, Imalumab, Imciromab, Imgatuzumab, Inclacumab, Indatuximab ravtansine, Indusatumab vedotin, Inebilizumab, Infliximab, Inolimomab, Inotuzumab ozogamicin, Intetumumab, Ipilimumab, Iratumumab, Isatuximab, Itolizumab, Ixekizumab, Keliximab, Labetuzumab, Lambrolizumab, Lampalizumab, Lanadelumab, Landogrozumab, Laprituximab emtansine, LBR-101/PF0442g7429, Lebrikizumab, Lemalesomab, Lendalizumab, Lenzilumab, Lerdelimumab, Lexatumumab, Libivirumab, Lifastuzumab vedotin, Ligelizumab, Lilotomab satetraxetan, Lintuzumab, Lirilumab, Lodelcizumab, Lokivetmab, Lorvotuzumab mertansine, Lucatumumab, Lulizumab pegol, Lumiliximab, Lumretuzumab, LY2951742, Mapatumumab, Margetuximab, Maslimomab, Matuzumab, Mavrilimumab, Mepolizumab, Metelimumab, Milatuzumab, Minretumomab, Mirvetuximab soravtansine, Mitumomab, Mogamulizumab, Monalizumab, Morolimumab, Motavizumab, Moxetumomab pasudotox, Muromonab-CD3, Nacolomab tafenatox, Namilumab, Naptumomab estafenatox, Naratuximab emtansine, Narnatumab, Natalizumab, Navicixizumab, Navivumab, Nebacumab, Necitumumab, Nemolizumab, Nerelimomab, Nesvacumab, Nimotuzumab, Nivolumab, Nofetumomab merpentan,

Obiltoxaximab, Obinutuzumab, Ocaratuzumab, Ocrelizumab, Odulimomab, Ofatumumab, Olaratumab, Olokizumab, Omalizumab, Onartuzumab, Ontuxizumab, Opicinumab, Oportuzumab monatox, Oregovomab, Orticumab, Otelixizumab, Otlertuzumab, Oxelumab, Ozanezumab, Ozoralizumab, Pagibaximab, Palivizumab, Pamrevlumab, Panitumumab, Pankomab, Panobacumab, Parsatuzumab, Pascolizumab, Pasotuxizumab, Pateclizumab, Patritumab, Pembrolizumab, Pemtumomab, Perakizumab, Pertuzumab, Pexelizumab, Pidilizumab, Pinatuzumab vedotin, Pintumomab, Placulumab, Plozalizumab, Pogalizumab, Polatuzumab vedotin, Ponezumab, Prezalizumab, Priliximab, Pritoxaximab, Pritumumab, PRO 140, Quilizumab, Racotumomab, Radretumab, Rafivirumab, Ralpancizumab, Ramucirumab, Ranibizumab, Raxibacumab, Refanezumab, Regavirumab, Reslizumab, Rilotumumab, Rinucumab, Risankizumab, Rituximab, Rivabazumab pegol, Robatumumab, Roledumab, Romosozumab, Rontalizumab, Rovalpituzumab tesirine, Rovelizumab, Ruplizumab, Sacituzumab govitecan, Samalizumab, Sapelizumab, Sarilumab, Satumomab pendetide, Secukinumab, Seribantumab, Setoxaximab, Sevirumab, SGN-CD19A, SGN-CD33A, Sibrotuzumab, Sifalimumab, Siltuximab, Simtuzumab, Siplizumab, Sirukumab, Sofituzumab vedotin, Solanezumab, Solitomab, Sonepcizumab, Sontuzumab, Stamulumab, Sulesomab, Suvizumab, Tabalumab, Tacatuzumab tetraxetan, Tadocizumab, Talizumab, Tamtuvetmab, Tanezumab, Taplitumomab paptox, Tarextumab, Tefibazumab, Telimomab aritox, Tenatumomab, Teneliximab, Teplizumab, Teprotumumab, Tesidolumab, Tetulomab, Tezepelumab, TGN1412, Ticilimumab, Tigatuzumab, Tildrakizumab, Timolumab, Tisotumab vedotin, TNX-650, Tocilizumab, Toralizumab, Tosatoxumab, Tositumomab, Tovetumab, Tralokinumab, Trastuzumab, Trastuzumab emtansine, TRBS07, Tregalizumab, Tremelimumab, Trevogrumab, Tucotuzumab celmoleukin, Tuvirumab, Ublituximab, Ulocuplumab, Urelumab, Urtoxazumab, Ustekinumab, Utomilumab, Vadastuximab talirine, Vandortuzumab vedotin, Vantictumab, Vanucizumab, Vapaliximab, Varlilumab, Vatelizumab, Vedolizumab, Veltuzumab, Vepalimomab, Vesencumab, Visilizumab, Vobarilizumab, Volociximab, Vorsetuzumab mafodotin, Votumumab, Xentuzumab, Zalutumumab, Zanolimumab, Zatuximab, Ziralimumab, and Zolimomab aritox or combinations thereof.

[0098] Examples of vaccines developed for viral diseases include but are not limited to: Hepatitis A vaccine, Hepatitis B vaccine, Hepatitis E vaccine, HPV vaccine, Influenza vaccine, Japanese encephalitis vaccine, MMR vaccine, MMRV vaccine, Polio vaccine, Rabies vaccine, Rotavirus vaccine, Varicella vaccine, Shingles vaccine, Smallpox vaccine, Yellow Fever vaccine, Adenovirus vaccine, Coxsackie B virus vaccine, Cytomegalovirus vaccine, Dengue vaccine for humans, Eastern Equine encephalitis virus vaccine for humans, Ebola vaccine, Enterovirus 71 vaccine, Epstein–Barr vaccine, Hepatitis C vaccine, HIV vaccine, HTLV-1 T-lymphotropic leukemia vaccine for humans, Marburg virus disease vaccine, Norovirus vaccine, Respiratory syncytial virus vaccine for humans, Severe acute respiratory syndrome (SARS) vaccine, West Nile virus vaccine for humans; Examples of bacterial diseases include but are not limited to: Anthrax vaccines, DPT vaccine, Q fever vaccine, Hib vaccine, Tuberculosis (BCG) vaccine, Meningococcal vaccine, Typhoid vaccine, Pneumococcal conjugate vaccine, Pneumococcal polysaccharide vaccine, Cholera vaccine, Caries vaccine, Ehrlichiosis vaccine, Leprosy vaccine, Lyme disease vaccine, Staphylococcus aureus vaccine, Streptococcus pyogenes vaccine, Syphilis vaccine, Tularemia vaccine, Yersinia pestis vaccine; Examples of parasitic diseases include but are not limited to: Malaria vaccine, Schistosomiasis vaccine, Chagas disease vaccine, Hookworm vaccine, Onchocerciasis river blindness vaccine for humans, Trypanosomiasis vaccine, Visceral leishmaniasis vaccine; Examples of non-infectious diseases include but are not limited to: Alzheimer's disease amyloid protein vaccine, Breast cancer vaccine, Ovarian cancer vaccine, Prostate cancer vaccine, Talimogene laherparepvec (T-VEC); also vaccines including but not limited to the following trade names: ACAM2000, ActHIB, Adacel, Afluria, AFLURIA QUADRIVALENT, Agriflu, BCG Vaccine, BEXSERO, Biothrax, Boostrix, Cervarix, Comvax, DAPTACEL, DECAVAC, Engerix-B, FLUAD, Fluarix, Fluarix Quadrivalent, Flublok, Flucelvax, Flucelvax Quadrivalent, FluLaval, FluMist, FluMist Quadrivalent, Fluvirin, Fluzone Quadrivalent, Fluzone, Fluzone High-Dose and Fluzone Intradermal, Gardasil, Gardasil 9, Havrix, Hiberix, Imovax, Infanrix, IPOL, Ixiaro, JE-Vax, KINRIX, Menactra, MenHibrix, Menomune-A/C/Y/W-135, Menveo, M-M-R II, M-M-Vax, Pediarix, PedvaxHIB, Pentacel, Pneumovax 23, Poliovax, Prevnar, Prevnar 13, ProQuad, Quadracel, Quadrivalent, RabAvert, Recombivax HB, ROTARIX, RotaTeq,

TENIVAC, TICE BCG, Tripedia, TRUMENBA, Twinrix, TYPHIM Vi, VAQTA, Varivax, Vaxchora, Vivotif, YF-Vax, Zostavax, and combinations thereof.

[0099] Examples of injectable drugs include but are not limited to: Ablavar (Gadofosveset Trisodium Injection), Abarelix Depot, Abobotulinumtoxin A Injection (Dysport), ABT-263, ABT-869, ABX-EFG, Accretropin (Somatropin Injection), Acetadote (Acetylcysteine Injection), Acetazolamide Injection (Acetazolamide Injection), Acetylcysteine Injection (Acetadote), Actemra (Tocilizumab Injection), Acthrel (Corticorelin Ovine Triflutate for Injection), Actummune, Activase, Acyclovir for Injection (Zovirax Injection), Adacel, Adalimumab, Adenoscan (Adenosine Injection), Adenosine Injection (Adenoscan), Adrenaclick, AdreView (Iobenguane 1123 Injection for Intravenous Use), Afluria, Ak-Fluor (Fluorescein Injection), Aldurazyme (Laronidase), Alglucerase Injection (Ceredase), Alkeran Injection (Melphalan Hcl Injection), Allopurinol Sodium for Injection (Aloprim), Aloprim (Allopurinol Sodium for Injection), Alprostadil, Alsuma (Sumatriptan Injection), ALTU-238, Amino Acid Injections, Aminosyn, Apidra, Apremilast, Alprostadil Dual Chamber System for Injection (Caverject Impulse), AMG 009, AMG 076, AMG 102, AMG 108, AMG 114, AMG 162, AMG 220, AMG 221, AMG 222, AMG 223, AMG 317, AMG 379, AMG 386, AMG 403, AMG 477, AMG 479, AMG 517, AMG 531, AMG 557, AMG 623, AMG 655, AMG 706, AMG 714, AMG 745, AMG 785, AMG 811, AMG 827, AMG 837, AMG 853, AMG 951, Amiodarone HCl Injection (Amiodarone HCl Injection), Amobarbital Sodium Injection (Amytal Sodium), Amytal Sodium (Amobarbital Sodium Injection), Anakinra, Anti-Abeta, Anti-Beta7, Anti-Beta20, Anti-CD4, Anti-CD20, Anti-CD40, Anti-IFNalpha, Anti-IL13, Anti-OX40L, Anti-oxLDS, Anti-NGF, Anti-NRP1, Arixtra, Amphadase (Hyaluronidase Inj), Ammonul (Sodium Phenylacetate and Sodium Benzoate Injection), Anaprox, Anzemet Injection (Dolasetron Mesylate Injection), Apidra (Insulin Glulisine [rDNA origin] Inj), Apomab, Aranesp (darbepoetin alfa), Argatroban (Argatroban Injection), Arginine Hydrochloride Injection (R-Gene 10, Aristocort, Aristospan, Arsenic Trioxide Injection (Trisenox), Articane HCl and Epinephrine Injection (Septocaine), Arzerra (Ofatumumab Injection), Asclera (Polidocanol Injection), Ataluren, Ataluren-DMD, Atenolol Inj (Tenormin I.V. Injection), Atracurium Besylate Injection (Atracurium Besylate Injection), Avastin, Azactam Injection (Aztreonam Injection), Azithromycin (Zithromax Injection), Aztreonam

Injection (Azactam Injection), Baclofen Injection (Lioresal Intrathecal), Bacteriostatic Water (Bacteriostatic Water for Injection), Baclofen Injection (Lioresal Intrathecal), Bal in Oil Ampules (Dimercarprol Injection), BayHepB, BayTet, Benadryl, Bendamustine Hydrochloride Injection (Treanda), Benztropine Mesylate Injection (Cogentin), Betamethasone Injectable Suspension (Celestone Soluspan), Bexxar, Bicillin C-R 900/300 (Penicillin G Benzathine and Penicillin G Procaine Injection), Blenoxane (Bleomycin Sulfate Injection), Bleomycin Sulfate Injection (Blenoxane), Boniva Injection (Ibandronate Sodium Injection), Botox Cosmetic (OnabotulinumtoxinA for Injection), BR3-FC, Bravelle (Urofollitropin Injection), Bretylium (Bretylium Tosylate Injection), Brevital Sodium (Methohexital Sodium for Injection), Brethine, Briobacept, BTT-1023, Bupivacaine HCl, Byetta, Ca-DTPA (Pentetate Calcium Trisodium Inj), Cabazitaxel Injection (Jevtana), Caffeine Alkaloid (Caffeine and Sodium Benzoate Injection), Calcijex Injection (Calcitrol), Calcitrol (Calcijex Injection), Calcium Chloride (Calcium Chloride Injection 10%), Calcium Disodium Versenate (Edetate Calcium Disodium Injection), Campath (Altemtuzumab), Camptosar Injection (Irinotecan Hydrochloride), Canakinumab Injection (Ilaris), Capastat Sulfate (Capreomycin for Injection), Capreomycin for Injection (Capastat Sulfate), Cardiolite (Prep kit for Technetium Tc99 Sestamibi for Injection), Carticel, Cathflo, Cefazolin and Dextrose for Injection (Cefazolin Injection), Cefepime Hydrochloride, Cefotaxime, Ceftriaxone, Cerezyme, Carnitor Injection, Caverject, Celestone Soluspan, Celsior, Cerebyx (Fosphenytoin Sodium Injection), Ceredase (Alglucerase Injection), Ceretec (Technetium Tc99m Exametazime Injection), Certolizumab, CF-101, Chloramphenicol Sodium Succinate (Chloramphenicol Sodium Succinate Injection), Chloramphenicol Sodium Succinate Injection (Chloramphenicol Sodium Succinate), Cholestagel (Colesevelam HCL), Choriogonadotropin Alfa Injection (Ovidrel), Cimzia, Cisplatin (Cisplatin Injection), Clolar (Clofarabine Injection), Clomiphine Citrate, Clonidine Injection (Duraclon), Cogentin (Benztropine Mesylate Injection), Colistimethate Injection (Coly-Mycin M), Coly-Mycin M (Colistimethate Injection), Compath, Conivaptan Hcl Injection (Vaprisol), Conjugated Estrogens for Injection (Premarin Injection), Copaxone, Corticorelin Ovine Triflutate for Injection (Acthrel), Corvert (Ibutilide Fumarate Injection), Cubicin (Daptomycin Injection), CF-101, Cyanokit (Hydroxocobalamin for Injection), Cytarabine Liposome Injection

(DepoCyt), Cyanocobalamin, Cytovene (ganciclovir), D.H.E. 45, Dacetuzumab, Dacogen (Decitabine Injection), Dalteparin, Dantrium IV (Dantrolene Sodium for Injection), Dantrolene Sodium for Injection (Dantrium IV), Daptomycin Injection (Cubicin), Darbepoietin Alfa, DDAVP Injection (Desmopressin Acetate Injection), Decavax, Decitabine Injection (Dacogen), Dehydrated Alcohol (Dehydrated Alcohol Injection), Denosumab Injection (Prolia), Delatestryl, Delestrogen, Delteparin Sodium, Depacon (Valproate Sodium Injection), Depo Medrol (Methylprednisolone Acetate Injectable Suspension), DepoCyt (Cytarabine Liposome Injection), DepoDur (Morphine Sulfate XR Liposome Injection), Desmopressin Acetate Injection (DDAVP Injection), Depo-Estradiol, Depo-Provera 104 mg/mL, Depo-Provera 150 mg/mL, Depo-Testosterone, Dexrazoxane for Injection, Intravenous Infusion Only (Totect), Dextrose/Electrolytes, Dextrose and Sodium Chloride Inj (Dextrose 5% in 0.9% Sodium Chloride), Dextrose, Diazepam Injection (Diazepam Injection), Digoxin Injection (Lanoxin Injection), Dilaudid-HP (Hydromorphone Hydrochloride Injection), Dimercarprol Injection (Bal in Oil Ampules), Diphenhydramine Injection (Benadryl Injection), Dipyridamole Injection (Dipyridamole Injection), DMOAD, Docetaxel for Injection (Taxotere), Dolasetron Mesylate Injection (Anzemet Injection), Doribax (Doripenem for Injection), Doripenem for Injection (Doribax), Doxercalciferol Injection (Hectorol Injection), Doxil (Doxorubicin Hcl Liposome Injection), Doxorubicin Hcl Liposome Injection (Doxil), Duraclon (Clonidine Injection), Duramorph (Morphine Injection), Dysport (Abobotulinumtoxin A Injection), Ecallantide Injection (Kalbitor), EC-Naprosyn (naproxen), Edetate Calcium Disodium Injection (Calcium Disodium Versenate), Edex (Alprostadil for Injection), Engerix, Edrophonium Injection (Enlon), Eliglustat Tartate, Eloxatin (Oxaliplatin Injection), Emend Injection (Fosaprepitant Dimeglumine Injection), Enalaprilat Injection (Enalaprilat Injection), Enlon (Edrophonium Injection), Enoxaparin Sodium Injection (Lovenox), Eovist (Gadoxetate Disodium Injection), Enbrel (etanercept), Enoxaparin, Epicel, Epinepherine, Epipen, Epipen Jr., Epratuzumab, Erbitux, Ertapenem Injection (Invanz), Erythropoieten, Essential Amino Acid Injection (Nephramine), Estradiol Cypionate, Estradiol Valerate, Etanercept, Exenatide Injection (Byetta), Evlotra, Fabrazyme (Adalsidase beta), Famotidine Injection, FDG (Fludeoxyglucose F 18 Injection), Feraheme (Ferumoxytol Injection), Feridex I.V.

(Ferumoxides Injectable Solution), Fertinex, Ferumoxides Injectable Solution (Feridex I.V.), Ferumoxytol Injection (Feraheme), Flagyl Injection (Metronidazole Injection), Fluarix, Fludara (Fludarabine Phosphate), Fludeoxyglucose F 18 Injection (FDG), Fluorescein Injection (Ak-Fluor), Follistim AQ Cartridge (Follitropin Beta Injection), Follitropin Alfa Injection (Gonal-f RFF), Follitropin Beta Injection (Follistim AQ Cartridge), Folotyn (Pralatrexate Solution for Intravenous Injection), Fondaparinux, Forteo (Teriparatide (rDNA origin) Injection), Fostamatinib, Fosaprepitant Dimeglumine Injection (Emend Injection), Foscarnet Sodium Injection (Foscavir), Foscavir (Foscarnet Sodium Injection), Fosphenytoin Sodium Injection (Cerebyx), Fospropofol Disodium Injection (Lusedra), Fragmin, Fuzeon (enfuvirtide), GA101, Gadobenate Dimeglumine Injection (Multihance), Gadofosveset Trisodium Injection (Ablavar), Gadoteridol Injection Solution (ProHance), Gadoversetamide Injection (OptiMARK), Gadoxetate Disodium Injection (Eovist), Ganirelix (Ganirelix Acetate Injection), Gardasil, GC1008, GDFD, Gemtuzumab Ozogamicin for Injection (Mylotarg), Genotropin, Gentamicin Injection, GENZ-112638, Golimumab Injection (Simponi Injection), Gonal-f RFF (Follitropin Alfa Injection), Granisetron Hydrochloride (Kytril Injection), Gentamicin Sulfate, Glatiramer Acetate, Glucagen, Glucagon, HAE1, Haldol (Haloperidol Injection), Havrix, Hectorol Injection (Doxercalciferol Injection), Hedgehog Pathway Inhibitor, Heparin, Herceptin, hG-CSF, Humalog, Human Growth Hormone, Humatrope, HuMax, Humegon, Humira, Humulin, Ibandronate Sodium Injection (Boniva Injection), Ibuprofen Lysine Injection (NeoProfen), Ibutilide Fumarate Injection (Corvert), Idamycin PFS (Idarubicin Hydrochloride Injection), Idarubicin Hydrochloride Injection (Idamycin PFS), Ilaris (Canakinumab Injection), Imipenem and Cilastatin for Injection (Primaxin I.V.), Imitrex, Incobotulinumtoxin A for Injection (Xeomin), Increlex (Mecasermin [rDNA origin] Injection), Indocin IV (Indomethacin Inj), Indomethacin Inj (Indocin IV), Infanrix, Innohep, Insulin, Insulin Aspart [rDNA origin] Inj (NovoLog), Insulin Glargine [rDNA origin] Injection (Lantus), Insulin Glulisine [rDNA origin] Inj (Apidra), Interferon alfa-2b, Recombinant for Injection (Intron A), Intron A (Interferon alfa-2b, Recombinant for Injection), Invanz (Ertapenem Injection), Invega Sustenna (Paliperidone Palmitate Extended-Release Injectable Suspension), Invirase (saquinavir mesylate), Iobenguane 1123 Injection for Intravenous Use (AdreView), Iopromide Injection (Ultravist), Ioversol

Injection (Optiray Injection), Iplex (Mecasermin Rinfabate [rDNA origin] Injection), Iprivask, Irinotecan Hydrochloride (Camptosar Injection), Iron Sucrose Injection (Venofer), Istodax (Romidepsin for Injection), Itraconazole Injection (Sporanox Injection), Jevtana (Cabazitaxel Injection), Jonexa, Kalbitor (Ecallantide Injection), KCL in D5NS (Potassium Chloride in 5% Dextrose and Sodium Chloride Injection), KCL in D5W, KCL in NS, Kenalog 10 Injection (Triamcinolone Acetonide Injectable Suspension), Kepivance (Palifermin), Keppra Injection (Levetiracetam), Keratinocyte, KFG, Kinase Inhibitor, Kineret (Anakinra), Kinlytic (Urokinase Injection), Kinrix, Klonopin (clonazepam), Kytril Injection (Granisetron Hydrochloride), lacosamide Tablet and Injection (Vimpat), Lactated Ringer's, Lanoxin Injection (Digoxin Injection), Lansoprazole for Injection (Prevacid I.V.), Lantus, Leucovorin Calcium (Leucovorin Calcium Injection), Lente (L), Leptin, Levemir, Leukine Sargramostim, Leuprolide Acetate, Levothyroxine, Levetiracetam (Keppra Injection), Lovenox, Levocarnitine Injection (Carnitor Injection), Lexiscan (Regadenoson Injection), Lioresal Intrathecal (Baclofen Injection), Liraglutide [rDNA] Injection (Victoza), Lovenox (Enoxaparin Sodium Injection), Lucentis (Ranibizumab Injection), Lumizyme, Lupron (Leuprolide Acetate Injection), Lusedra (Fospropofol Disodium Injection), Maci, Magnesium Sulfate (Magnesium Sulfate Injection), Mannitol Injection (Mannitol IV), Marcaine (Bupivacaine Hydrochloride and Epinephrine Injection), Maxipime (Cefepime Hydrochloride for Injection), MDP Multidose Kit of Technetium Injection (Technetium Tc99m Medronate Injection), Mecasermin [rDNA origin] Injection (Increlex), Mecasermin Rinfabate [rDNA origin] Injection (Iplex), Melphalan Hcl Injection (Alkeran Injection), Methotrexate, Menactra, Menopur (Menotropins Injection), Menotropins for Injection (Repronex), Methohexital Sodium for Injection (Brevital Sodium), Methyldopate Hydrochloride Injection, Solution (Methyldopate Hcl), Methylene Blue (Methylene Blue Injection), Methylprednisolone Acetate Injectable Suspension (Depo Medrol), MetMab, Metoclopramide Injection (Reglan Injection), Metrodin (Urofollitropin for Injection), Metronidazole Injection (Flagyl Injection), Miacalcin, Midazolam (Midazolam Injection), Mimpara (Cinacalet), Minocin Injection (Minocycline Inj), Minocycline Inj (Minocin Injection), Mipomersen, Mitoxantrone for Injection Concentrate (Novantrone), Morphine Injection (Duramorph), Morphine Sulfate XR Liposome Injection (DepoDur), Morrhuate Sodium (Morrhuate

Sodium Injection), Motesanib, Mozobil (Plerixafor Injection), Multihance (Gadobenate Dimeglumine Injection), Multiple Electrolytes and Dextrose Injection, Multiple Electrolytes Injection, Mylotarg (Gemtuzumab Ozogamicin for Injection), Myozyme (Alglucosidase alfa), Nafcillin Injection (Nafcillin Sodium), Nafcillin Sodium (Nafcillin Injection), Naltrexone XR Inj (Vivitrol), Naprosyn (naproxen), NeoProfen (Ibuprofen Lysine Injection), Nandrol Decanoate, Neostigmine Methylsulfate (Neostigmine Methylsulfate Injection), NEO-GAA, NeoTect (Technetium Tc 99m Depreotide Injection), Nephramine (Essential Amino Acid Injection), Neulasta (pegfilgrastim), Neupogen (Filgrastim), Novolin, Novolog, NeoRecormon, Neutrexin (Trimetrexate Glucuronate Inj), NPH (N), Nexterone (Amiodarone HCl Injection), Norditropin (Somatropin Injection), Normal Saline (Sodium Chloride Injection), Novantrone (Mitoxantrone for Injection Concentrate), Novolin 70/30 Innolet (70% NPH, Human Insulin Isophane Suspension and 30% Regular, Human Insulin Injection), NovoLog (Insulin Aspart [rDNA origin] Inj), Nplate (romiplostim), Nutropin (Somatropin (rDNA origin) for Inj), Nutropin AQ, Nutropin Depot (Somatropin (rDNA origin) for Inj), Octreotide Acetate Injection (Sandostatin LAR), Ocrelizumab, Ofatumumab Injection (Arzerra), Olanzapine Extended Release Injectable Suspension (Zyprexa Relprevv), Omnitarg, Omnitrope (Somatropin [rDNA origin] Injection), Ondansetron Hydrochloride Injection (Zofran Injection), OptiMARK (Gadoversetamide Injection), Optiray Injection (Ioversol Injection), Orencia, Osmitrol Injection in Aviva (Mannitol Injection in Aviva Plastic Vessel 250), Osmitrol Injection in Viaflex (Mannitol Injection in Viaflex Plastic Vessel 250), Osteoprotegrin, Ovidrel (Choriogonadotropin Alfa Injection), Oxacillin (Oxacillin for Injection), Oxaliplatin Injection (Eloxatin), Oxytocin Injection (Pitocin), Paliperidone Palmitate Extended-Release Injectable Suspension (Invega Sustenna), Pamidronate Disodium Injection (Pamidronate Disodium Injection), Panitumumab Injection for Intravenous Use (Vectibix), Papaverine Hydrochloride Injection (Papaverine Injection), Papaverine Injection (Papaverine Hydrochloride Injection), Parathyroid Hormone, Paricalcitol Injection Fliptop Vial (Zemplar Injection), PARP Inhibitor, Pediarix, PEGIntron, Peginterferon, Pegfilgrastim, Penicillin G Benzathine and Penicillin G Procaine, Pentetate Calcium Trisodium Inj (Ca-DTPA), Pentetate Zinc Trisodium Injection (Zn-DTPA), Pepcid Injection (Famotidine Injection), Pergonal, Pertuzumab, Phentolamine

Mesylate (Phentolamine Mesylate for Injection), Physostigmine Salicylate (Physostigmine Salicylate (injection)), Physostigmine Salicylate (injection) (Physostigmine Salicylate), Piperacillin and Tazobactam Injection (Zosyn), Pitocin (Oxytocin Injection), Plasma-Lyte 148 (Multiple Electrolytes Inj), Plasma-Lyte 56 and Dextrose (Multiple Electrolytes and Dextrose Injection in Viaflex, Plastic Vessel 250), PlasmaLyte, Plerixafor Injection (Mozobil), Polidocanol Injection (Asclera), Potassium Chloride, Pralatrexate Solution for Intravenous Injection (Folotyn), Pramlintide Acetate Injection (Symlin), Premarin Injection (Conjugated Estrogens for Injection), Prep kit for Technetium Tc99 Sestamibi for Injection (Cardiolite), Prevacid I.V. (Lansoprazole for Injection), Primaxin I.V. (Imipenem and Cilastatin for Injection), Prochymal, Procrit, Progesterone, ProHance (Gadoteridol Injection Solution), Prolia (Denosumab Injection), Promethazine HCl Injection (Promethazine Hydrochloride Injection), Propranolol Hydrochloride Injection (Propranolol Hydrochloride Injection), Quinidine Gluconate Injection (Quinidine Injection), Quinidine Injection (Quinidine Gluconate Injection), R-Gene 10 (Arginine Hydrochloride Injection), Ranibizumab Injection (Lucentis), Ranitidine Hydrochloride Injection (Zantac Injection), Raptiva, Reclast (Zoledronic Acid Injection), Recombivarix HB, Regadenoson Injection (Lexiscan), Reglan Injection (Metoclopramide Injection), Remicade, Renagel, Renvela (Sevelamer Carbonate), Repronex (Menotropins for Injection), Retrovir IV (Zidovudine Injection), rhApo2L/TRAIL, Ringer's and 5% Dextrose Injection (Ringers in Dextrose), Ringer's Injection (Ringers Injection), Rituxan, Rituximab, Rocephin (ceftriaxone), Rocuronium Bromide Injection (Zemuron), Roferon-A (interferon alfa-2a), Romazicon (flumazenil), Romidepsin for Injection (Istodax), Saizen (Somatropin Injection), Sandostatin LAR (Octreotide Acetate Injection), Sclerostin Ab, Sensipar (cinacalcet), Sensorcaine (Bupivacaine HCl Injections), Septocaine (Articane HCl and Epinephrine Injection), Serostim LQ (Somatropin (rDNA origin) Injection), Simponi Injection (Golimumab Injection), Sodium Acetate (Sodium Acetate Injection), Sodium Bicarbonate (Sodium Bicarbonate 5% Injection), Sodium Lactate (Sodium Lactate Injection in AVIVA), Sodium Phenylacetate and Sodium Benzoate Injection (Ammonul), Somatropin (rDNA origin) for Inj (Nutropin), Sporanox Injection (Itraconazole Injection), Stelara Injection (Ustekinumab), Stemgen, Sufenta (Sufentanil Citrate Injection), Sufentanil Citrate Injection (Sufenta), Sumavel,

Sumatriptan Injection (Alsuma), Symlin, Symlin Pen, Systemic Hedgehog Antagonist, Synvisc-One (Hylan G-F 20 Single Intra-articular Injection), Tarceva, Taxotere (Docetaxel for Injection), Technetium Tc 99m, Telavancin for Injection (Vibativ), Temsirolimus Injection (Torisel), Tenormin I.V. Injection (Atenolol Inj), Teriparatide (rDNA origin) Injection (Forteo), Testosterone Cypionate, Testosterone Enanthate, Testosterone Propionate, Tev-Tropin (Somatropin, rDNA Origin, for Injection), tgAAC94, Thallous Chloride, Theophylline, Thiotepa (Thiotepa Injection), Thymoglobulin (Anti-Thymocyte Globulin (Rabbit), Thyrogen (Thyrotropin Alfa for Injection), Ticarcillin Disodium and Clavulanate Potassium Galaxy (Timentin Injection), Tigan Injection (Trimethobenzamide Hydrochloride Injectable), Timentin Injection (Ticarcillin Disodium and Clavulanate Potassium Galaxy), TNKase, Tobramycin Injection (Tobramycin Injection), Tocilizumab Injection (Actemra), Torisel (Temsirolimus Injection), Totect (Dexrazoxane for Injection, Intravenous Infusion Only), Trastuzumab-DM1, Travasol (Amino Acids (Injection)), Treanda (Bendamustine Hydrochloride Injection), Trelstar (Triptorelin Pamoate for Injectable Suspension), Triamcinolone Acetonide, Triamcinolone Diacetate, Triamcinolone Hexacetonide Injectable Suspension (Aristospan Injection 20 mg), Triesence (Triamcinolone Acetonide Injectable Suspension), Trimethobenzamide Hydrochloride Injectable (Tigan Injection), Trimetrexate Glucuronate Inj (Neutrexin), Triptorelin Pamoate for Injectable Suspension (Trelstar), Twinject, Trivaris (Triamcinolone Acetonide Injectable Suspension), Trisenox (Arsenic Trioxide Injection), Twinrix, Typhoid Vi, Ultravist (Iopromide Injection), Urofollitropin for Injection (Metrodin), Urokinase Injection (Kinlytic), Ustekinumab (Stelara Injection), Ultralente (U), Valium (diazepam), Valproate Sodium Injection (Depacon), Valtropin (Somatropin Injection), Vancomycin Hydrochloride (Vancomycin Hydrochloride Injection), Vancomycin Hydrochloride Injection (Vancomycin Hydrochloride), Vaprisol (Conivaptan Hcl Injection), VAQTA, Vasovist (Gadofosveset Trisodium Injection for Intravenous Use), Vectibix (Panitumumab Injection for Intravenous Use), Venofer (Iron Sucrose Injection), Verteporfin Inj (Visudyne), Vibativ (Telavancin for Injection), Victoza (Liraglutide [rDNA] Injection), Vimpat (lacosamide Tablet and Injection), Vinblastine Sulfate (Vinblastine Sulfate Injection), Vincasar PFS (Vincristine Sulfate Injection), Victoza, Vincristine Sulfate (Vincristine Sulfate Injection),

Visudyne (Verteporfin Inj), Vitamin B-12, Vivitrol (Naltrexone XR Inj), Voluven (Hydroxyethyl Starch in Sodium Chloride Injection), Xeloda, Xenical (orlistat), Xeomin (Incobotulinumtoxin A for Injection), Xolair, Zantac Injection (Ranitidine Hydrochloride Injection), Zemplar Injection (Paricalcitol Injection Fliptop Vial), Zemuron (Rocuronium Bromide Injection), Zenapax (daclizumab), Zevalin, Zidovudine Injection (Retrovir IV), Zithromax Injection (Azithromycin), Zn-DTPA (Pentetate Zinc Trisodium Injection), Zofran Injection (Ondansetron Hydrochloride Injection), Zingo, Zoledronic Acid for Inj (Zometa), Zoledronic Acid Injection (Reclast), Zometa (Zoledronic Acid for Inj), Zosyn (Piperacillin and Tazobactam Injection), Zyprexa Relprevv (Olanzapine Extended Release Injectable Suspension) and combinations thereof.

Example

[0100] Example 1- Insertion Tube Surface Finish

[0101] A strip (3 mm x 75 mm) of 22 µm cellulose acetate replicating tape (Ted Pella, Inc., Redding CA) was applied to the inner surface of several exemplary insertion tubes. The insertion tubes were formed of stainless steel and were prepared generally according to the teachings of U.S. Patent No. 10,369,292 to LaRose. The interior of insertion tubes 1 and 2 were surface treated or otherwise finished to reduce or minimize any asperities located within the tubes. The insertion tubes were wetted with acetone and allowed to dry. The strips of cellulose acetate were then removed from the insertion tubes using forceps. The strips were mounted on slides. The replicating tape surfaces were measured on a Keyence VK-X100 3D laser scanning microscope (Keyence Corporation, Osaka, Japan) using a 50X objective (200 µm x 270 µm field of view), a 2.5 µm S-filter, a 0.1 mm L-filter cut off wavelength, and a curved surface tilt correction. The average surface roughness (S_a) and average kurtosis (S_{ku}) were calculated per ISO 25178-2:2012. The data is set forth in Table 1.

[0102] Table 1 shows desirable surface parameters for Insertion Tubes 1 and 2, which resulted in successful insertions of the stoppers, as indicated by the helium leak rate and the number of lines observed on the front sealing rib of the stopper. In contrast, Insertion Tubes 3, 4 and 5 did not show desirable surface parameters, and did not result in a successful insertion of the stopper.

Table 1

Insertion Tube	Tube Body		Transition Zone	Average Number of Lines Observed on the Front Sealing Rib of the Stopper	Average Helium Leak Rate (sccs)
	Average Surface Roughness (S_a) (nm)	Average Kurtosis (S_{ku})	Average Surface Roughness (S_a)(nm)		
Insertion Tube 1	46	3.1	97	9	$7.366x10^{-9}$
Insertion Tube 2	101,103[1]	3.9, 5.1	195, 269	1	$2.077x10^{-9}$
Insertion Tube 3	37, 33	9.5, 12.8	450, 482	37	$2.58x10^{-7}$
Insertion Tube 4	40, 121	12.9, 13.4	428	27	$3.31x10^{-7}$
Insertion Tube 5	30, 43	8.8, 11.6	514	22	$3.16x10^{-8}$

1. In some samples two measurements were reported.

[0103] The invention of this application has been described above both generically and with regard to specific embodiments. It will be apparent to those skilled in the art that various modifications and variations can be made in the embodiments without departing from the scope of the disclosure. Thus, it is intended that the embodiments cover the modifications and variations of this invention provided they come within the scope of the appended claims and their equivalents.

WHAT IS CLAIMED IS

1. A method for inserting a lubricant free stopper into a lubricant free barrel, the method comprising:

(A) inserting a stopper that includes at least one sealing rib into a placement region located at a proximal end of an insertion tube, the insertion tube having a body connected to the placement region through a transition zone;

(B) lowering the body of the insertion tube into a syringe barrel having a barrel flange to a position located past the barrel flange;

(C) maneuvering the stopper to a distal opening of the insertion tube using an insertion pin;

(D) retracting the insertion tube while the stopper remains in a fixed position within the syringe barrel by the insertion pin, wherein the stopper is securely positioned within the syringe barrel; and

(E) fully retracting the insertion pin and the insertion tube from the barrel to form a stoppered syringe,

wherein at least the stopper, the insertion tube, the body of the insertion tube, the syringe barrel, the barrel flange, and the insertion pin are free or substantially free of lubricants.

2. The method of claim 1, wherein the insertion tube has an average surface roughness (Sa) from about 20 nm to about 400 nm.

3. The method of claim 1 or claim 2, wherein body of the insertion tube has an average kurtosis (S_{ku}) less than about 8.

4. The method of any one of claims 1-3, wherein the stopper is inserted into the insertion tube at a peak insertion force ranging from about 10 N to about 200 N.

5. The method of any one of claims 1-4, wherein the stopper includes at least one sealing rib and the sealing rib is has a line count of less than 30.

6. The method of any one of claims 1-5, wherein the stoppered syringe has a helium leak rate that is not greater than 6 x 10^{-6} sccs.

7. The method of any one of claims 1-6, wherein step (A) and step (B) occur sequentially or simultaneously.

8. The method of any one of claims 1-7, wherein in step (B), a gap is located between the insertion tube and an inner surface of the barrel to allow for pressure venting.

9. The method of any one of claims 1-8, wherein in step (D) the insertion tube is retracted prior to the insertion pin.

10. The method of any one of claims 1-9, wherein in step (E) the insertion tube and the insertion pin are retracted from the barrel sequentially or simultaneously.

11. The method of any one of claims 1-10, wherein the stopper comprises an elastomeric body and a polymer layer thereon.

12. The method of claim 11, wherein the polymer layer comprises an expanded fluoropolymer.

13. The method of claim 12, wherein the expanded fluoropolymer comprises an expanded polytetrafluoroethylene.

14. The method of any one of claims 1-10, further comprising delivering a therapeutic compound to the syringe barrel prior to lowering the insertion tube into the syringe barrel.

15. The method of claim 14, wherein the therapeutic substance contains therein a biologic, a therapeutic compound, or a combination thereof.

16. The method of claim 14, wherein an amount of particles in the barrel is less than about 600 particles / mL for particles greater than 10 μm in size when measured in water for injection (WFI).

17. The method of claim 14, wherein an amount of particles in the barrel is less than 60 particles /mL for particles greater than 25 μm in size when measured in water for injection (WFI).

18. The method of any one of claims 1-10 and 15, wherein the insertion tube has been electropolished, extrude honed, or a combination thereof.

19. A system comprising:

(A) an insertion tube having:

a placement region having a diameter for receiving a stopper from a stopper feeder;

a body having a diameter that is smaller than the diameter of the placement region; and

a transition zone having a tapered angle for transitioning the stopper from the placement region to the insertion tube body;

(B) an insertion pin for maneuvering the stopper through the insertion tube; and

(C) a barrel or cartridge tube having an inner surface for receiving the stopper from the insertion tube and a therapeutic substance from a therapeutic feeder,

wherein (A) to (C) comprise a system to form a pre-filled syringe or cartridge, and

wherein the system and the pre-filled syringe are lubricant free or substantially lubricant free.

20. The system of claim 19, wherein the taper angle is between about 1 degree and about 20 degrees.

21. The system of claim 19 or claim 20, wherein the insertion tube has an average surface roughness (Sa) from about 20 nm to about 400 nm.

22. The system of any one of claims 19-21, wherein the insertion tube body has an average kurtosis (Sku) less than about 8.

23. The system of any one of claims 19-22, wherein the insertion tube has been electropolished, extrude honed, or a combination thereof.

24. The system of any one of claims 19-23, wherein the therapeutic substance contains therein a biologic, a therapeutic compound, or a combination thereof.

25. The system of any one of claims 19-24, wherein the stopper comprises an elastomeric body and a polymer layer at least partially covering the elastomeric body.

26. The system of claim 25, wherein the polymer layer comprises an expanded fluoropolymer.

27. The system of claim 26, wherein the expanded fluoropolymer comprises an expanded polytetrafluoroethylene.

28. A method for inserting a lubricant free stopper into a lubricant free cartridge tube, the method comprising:

(A) inserting a stopper that includes at least one sealing rib into a placement region located at a proximal end of an insertion tube, the insertion tube having a body connected to the placement region through a transition zone;

(B) lowering the body of the insertion tube into a cartridge tube having a end portion to a position located past the top of the cartridge tube;

(C) maneuvering the stopper to a distal opening of the insertion tube using an insertion pin;

(D) retracting the insertion tube while the stopper remains in a fixed position within the cartridge tube by the insertion pin, wherein the stopper is securely positioned within the cartridge tube; and

(E) fully retracting the insertion pin and the insertion tube from the cartridge tube to form a stoppered cartridge,

wherein at least the stopper, the insertion tube, the body of the insertion tube, the cartridge tube, the top of the cartridge tube, and the insertion pin are free or substantially free of lubricants.

29. The method of claim 28, wherein the stopper is inserted into the insertion tube at a peak insertion force ranging from about 10 N to about 200 N.

30. The method of any claim 28 or claim 29, wherein the stopper includes at least one sealing rib and the sealing rib has a line count of less than 30.

31. The method of any one of claims 27-30, wherein step (A) and step (B) occur sequentially or simultaneously.

32. The method of any one of claims 28-31, wherein in step (B), a gap is located between the insertion tube and an inner surface of the cartridge tube to allow for pressure venting.

33. The method of any one of claims 28-32, wherein in step (D) the insertion tube is retracted prior to the insertion pin.

34. The method of any one of claims 28-33, wherein in step (E) the insertion tube and the insertion pin are retracted sequentially or simultaneously.

35. The method of any one of claims 28-34, wherein the stopper comprises an elastomeric body and a polymer layer thereon.

36 The method of claim 35, wherein the polymer layer comprises an expanded fluoropolymer.

37. The method of claim 36, wherein the expanded fluoropolymer comprises an expanded polytetrafluoroethylene.

38. The method of any one of claims 28-37, further comprising delivering a therapeutic compound to the cartridge tube prior to lowering the insertion tube into the cartridge tube.

39. The method of claim 38, wherein the therapeutic substance contains therein a biologic, a therapeutic compound, or a combination thereof.

40. The method of any one of claims 28-39, wherein the insertion tube has been electropolished, extrude honed, or a combination thereof.

41. The method of any one of claims 28-40, wherein the insertion tube has an average surface roughness (Sa) from about 20 nm to about 400 nm.

42. The method of any one of claims 28-41, wherein body of the insertion tube has an average kurtosis (S_{ku}) less than about 8.

43. The method of any one of claims 28-42, wherein the cartridge has a helium leak rate that is not greater than 6×10^{-6} sccs.