METHOD OF ASSESSING STOPPER MOVEMENT IN A DRUG DELIVERY DEVICE

TECHNICAL FIELD

[0001] This disclosure generally relates to an injection device for drug delivery for the injection device. More particularly, the disclosure generally relates to a method of assessing stopper movement in a drug delivery device, such as a syringe, and determining any risk of drug product contamination due to a breach in container closure integrity (CCI).

BACKGROUND

[0002] As is known in the art, syringes are medical delivery devices used to administer a medicament to a patient. Syringes are often marketed either in pre-filled form (i.e., pre-filled syringes), wherein a set dosage of medicament is already provided therein, or they are empty and intended to be filled from a vial or other source of medicament by an end user at the time administration of the medicament is desired.

[0003] Syringes often include a barrel portion adapted to retain the medicament. The distal end of the barrel is often configured to include and/or mate with a conventional piercing element, such as a pointed needle cannula or a blunt ended cannula, to deliver the medicament contained in the barrel. The piercing element may be made of steel, plastic, or any other suitable material. A plunger rod may be inserted through the open proximal end of the syringe barrel and, through its engagement with an elastomeric or rubber-like stopper element fitted in a substantially fluid-tight manner within the interior of the syringe barrel, a user can apply manual force to the plunger to deliver the medicament through the piercing element.

[0004] It may be desirable or required, to sterilize the external surfaces of the syringe while maintaining container closure integrity (CCI) such that the medicament or drug product contained within the syringe barrel is not contaminated. External sterilization typically occurs after the pre-filled syringe has been filled, fully assembled, and located in at least some portion(s) of its final packaging. For some indications of use, such as certain ophthalmic indications, federal regulations may require external sterilization under certain conditions, parameters, and/or results.

[0005] However, due to movement of the pre-filled syringes or components thereof due to pressure changes and other conditions that may occur during the manufacturing, assembly, and external sterilization processes, and due to various shipping, handling, and transporting conditions, one or more components of the pre-filled syringes, such as the stoppers, may move within the pre-filled syringes. In addition, external sterilization of the pre-filled syringes may pose further challenges. For example, the stoppers may move within the syringe barrel due to various conditions of the external sterilization process, such as pressure differences that may occur during external sterilization. If the amount of movement of the stopper exceeds the sterile barrier height of the stopper (i.e. the stopper rib-to-rib distance) prior to external sterilization, a breach in container closure integrity may occur, and the medicament or drug product within a cavity of the pre-filled syringe may potentially be contaminated due to the medicament or drug product coming into contact with the non-sterile surfaces of the syringe barrel.

[0006] Conventional methods for indirectly analyzing the risk of drug product contamination due to stopper movement and related container closure integrity breach issues exist. However, conventional methods for assessing stopper movement and analyzing the risk of drug product contamination only provide an indirect analysis because they rely on measuring stopper movement under simulated conditions. Various assumptions and theoretical parameters incorporated in existing simulation methods not only create ambiguity, but also fail to provide an accurate and commercially representative assessment of stopper movement and risk of drug product contamination in pre-filled syringes. Therefore, there is a need for an improved and accurate method of directly assessing stopper movement in pre-filled syringes and determining any risk of drug product contamination due to breach of container closure integrity.

[0007] The present disclosure sets forth approaches embodying advantageous alternatives to existing methods, and that may address one or more of the challenges or needs mentioned herein, as well as provide other benefits and advantages.

SUMMARY

[0008] According to an embodiment of the present disclosure, a method of assessing stopper movement in a syringe is provided, the syringe comprising a syringe barrel and a stopper movably disposed within the syringe barrel. The method comprises inoculating a biological particulate through an open proximal end of the syringe barrel such that the biological particulate covers at least a portion of an interface between a proximal face of the stopper and an inner wall of the syringe barrel. A cavity of the syringe contains a fill volume of liquid. The method also comprises subjecting the syringe to one or more conditions, extracting the fill volume of liquid from the cavity of the syringe, performing a sterility test on the extracted fill volume of liquid, and determining stopper movement in the syringe based on the sterility test.

[0009] In some embodiments, subjecting the syringe to one or more conditions may comprise at least one of: externally sterilizing the syringe, subjecting the syringe to shipping and handling conditions, or performing a manufacturing process with the syringe. In some embodiments, subjecting the syringe to one or more conditions may comprise externally sterilizing the syringe, and externally sterilizing the syringe may comprise placing the syringe in a sterilization chamber, introducing a dose of sterilant gas into the sterilization chamber and applying a predetermined vacuum level, holding the vacuum level for a predetermined dwell time, and purging the sterilization chamber of at least substantially all of the sterilant gas.

[0010] In some embodiments, the stopper may comprise a body portion having a generally cylindrical sidewall and one or more ribs projecting radially outwardly from the sidewall of the body portion near the proximal face of the stopper. The one or more ribs of the stopper may be configured to form a fluid-tight relationship with the cavity of the syringe. In some embodiments, the method may further comprise inoculating the biological particulate through the open proximal end of the syringe barrel such that the biological particulate covers at least a portion of an interface between the one or more ribs near the proximal face of the stopper and the inner wall of the syringe barrel.

[0011] In some embodiments, the biological particulate may be inoculated at a plurality of locations around a diameter of the proximal face of the stopper along the interface between the proximal face of the stopper and the inner wall of the syringe barrel. In some embodiments, the biological particulate may comprise at least one of: a microorganism, a fungus, a bacterium, a spore, a virus, a biological cell, a biological antigen, a protein, or a protein antigen.

[0012] In other embodiments, performing a sterility test on the extracted liquid may comprise suspending the extracted liquid into a testing medium containing Trypticase Soy Broth (TSB) or Fluid Thioglycollate Medium (FTM) and determining whether the extracted liquid contains the biological particulate. A presence of the biological particulate in the extracted liquid may be indicative of stopper movement in the syringe. In other embodiments, the fill volume of liquid may comprise a testing medium containing Trypticase Soy Broth (TSB) or Fluid Thioglycollate Medium (FTM), and performing a sterility test on the extracted liquid may comprise determining whether the extracted liquid contains the biological particulate.

[0013] In some embodiments, the syringe barrel may comprise a distal end configured to support a needle. The open proximal end of the syringe barrel may be configured to receive a plunger rod that is configured to push the stopper in a distal direction towards the distal end of the syringe barrel. In some embodiments, the syringe may be a pre-filled syringe, and the syringe barrel of the pre-filled syringe may be configured to contain a medicament. In other embodiments, the proximal face of the stopper may include a convex surface. In yet another embodiment, the proximal face of the stopper may include a plurality of protrusions protruding axially from the proximal face. In some embodiments, the method may further comprise identifying a risk of drug product contamination based at least on the determined stopper movement. The risk of drug product contamination may exist when a distance moved by the stopper is greater than or equal to an axial length of the stopper.

[0014] According to another embodiment of the present disclosure, a method of determining a risk of drug product contamination in a syringe is provided, the syringe comprising a syringe barrel and a stopper movably disposed within the syringe barrel. The method comprises inoculating a biological particulate through an open proximal end of the syringe barrel such that the biological particulate covers at least a portion of an interface between a proximal face of the stopper and an inner wall of the

syringe barrel. A cavity of the syringe contains a fill volume of liquid, and the biological particulate comprises at least one of: a microorganism, a fungus, a bacterium, a spore, a virus, a biological cell, a biological antigen, a protein, or a protein antigen. The method also comprises subjecting the syringe to one or more conditions, extracting the fill volume of liquid from the cavity of the syringe, performing a sterility test on the extracted fill volume of liquid, determining stopper movement in the syringe based on the sterility test, and identifying a risk of drug product contamination based at least on the determined stopper movement. The risk of drug product contamination exists when a distance moved by the stopper is greater than or equal to an axial length of the stopper.

[0015] In some embodiments, subjecting the syringe to one or more conditions may comprise at least one of: externally sterilizing the syringe, subjecting the syringe to shipping and handling conditions, or performing a manufacturing process with the syringe. In other embodiments, subjecting the syringe to one or more conditions may comprise externally sterilizing the syringe, and externally sterilizing the syringe may comprise placing the syringe in a sterilization chamber, introducing a dose of sterilant gas into the sterilization chamber and applying a predetermined vacuum level, holding the vacuum level for a predetermined dwell time, and purging the sterilization chamber of at least substantially all of the sterilant gas.

[0016] In some embodiments, the stopper may comprise a body portion having a generally cylindrical sidewall and one or more ribs projecting radially outwardly from the sidewall of the body portion near the proximal face of the stopper. The one or more ribs of the stopper may be configured to form a fluid-tight relationship with the cavity of the syringe. In some embodiments, the method may further comprise inoculating the biological particulate through the open proximal end of the syringe barrel such that the biological particulate covers at least a portion of an interface between the one or more ribs near the proximal face of the stopper and the inner wall of the syringe barrel.

[0017] In some embodiments, the biological particulate may be inoculated at a plurality of locations around a diameter of the proximal face of the stopper along the interface between the proximal face of the stopper and the inner wall of the syringe barrel. In other embodiments, performing a sterility test on the extracted liquid may comprise suspending the extracted liquid into a testing medium containing Trypticase Soy Broth (TSB) or Fluid Thioglycollate Medium (FTM), and determining whether the extracted liquid contains the biological particulate. A presence of the biological particulate in the extracted liquid may be indicative of stopper movement in the syringe. In other embodiments, the fill volume of liquid may comprise a testing medium containing Trypticase Soy Broth (TSB) or Fluid Thioglycollate Medium (FTM), and performing a sterility test on the extracted liquid may comprise determining whether the extracted liquid contains the biological particulate.

[0018] In some embodiments, the syringe barrel may comprise a distal end configured to support a needle. The open proximal end of the syringe barrel may be configured to receive a plunger rod that is configured to push the stopper in a distal direction towards the distal end of the syringe barrel. In some embodiments, the syringe may be a pre-filled syringe, and the syringe barrel of the pre-filled syringe may be configured to contain a medicament. In other embodiments, the proximal face of the stopper may include a convex surface. In yet another embodiment, the proximal face of the stopper may include a plurality of protrusions protruding axially from the proximal face.

BRIEF DESCRIPTION OF THE DRAWINGS

[0019] It is believed that the disclosure will be more fully understood from the following description taken in conjunction with the accompanying drawings. Some of the drawings may have been simplified by the omission of selected elements for the purpose of more clearly showing other elements. Such omissions of elements in some drawings are not necessarily indicative of the presence or absence of particular elements in any of the exemplary embodiments, except as may be explicitly delineated in the corresponding written description. Also, none of the drawings is necessarily to scale.

[0020] Fig. 1 is a front view of an exemplary drug delivery device, according to various embodiments of the present disclosure.

[0021] Fig. 2 is an exploded cross-sectional view of an exemplary syringe barrel of the exemplary drug delivery device of Fig. 1, according to various embodiments of the present disclosure.

[0022] Fig. 3 is a cross-sectional view of the exemplary syringe barrel of Fig. 2 that is inoculated with a biological particulate using an exemplary method, according to various embodiments of the present disclosure.

[0023] Fig. 4 is a cross-sectional view of the exemplary syringe barrel of Fig. 2 that is inoculated with a biological particulate using another exemplary method, according to various embodiments of the present disclosure.

[0024] Fig. 5 is a cross-sectional view of the exemplary syringe barrel of Fig. 2 that is inoculated with a biological particulate using another exemplary method, according to various embodiments of the present disclosure.

[0025] Fig. 6A is a perspective view of another exemplary stopper, according to various embodiments of the present disclosure.

[0026] Fig. 6B is a perspective view of another exemplary plunger rod configured to engage with the exemplary stopper of Fig. 6A, according to various embodiments of the present disclosure.

[0027] Fig. 7A is a perspective view of another exemplary stopper, according to various embodiments of the present disclosure.

[0028] Fig. 7B is a perspective view of another exemplary plunger rod configured to engage with the exemplary stopper of Fig. 7A, according to various embodiments of the present disclosure.

[0029] Fig. 8 is a flowchart illustrating an exemplary method of assessing stopper movement in a pre-filled syringe, according to various embodiments of the present disclosure.

[0030] Fig. 9 is a flowchart illustrating an exemplary method of determining a risk of drug product contamination in a pre-filled syringe, according to various embodiments of the present disclosure.

DETAILED DESCRIPTION

[0031] The present disclosure generally relates to injection devices which can be safely and reliably activated by a user for administering a drug, or in the case where a patient is the user, self-administering a drug. More particularly, the disclosure generally relates to approaches for assessing movement of a component of a drug delivery device, which, in some examples, includes a stopper (also referred to as “a plunger stopper”) of a syringe. The drug delivery device and the injection device may be a syringe, such as a pre-filled syringe containing a medicament. Additionally, the disclosure generally relates to approaches for identifying and/or determining a risk of drug product contamination of a drug delivery device, which, in some examples, includes a syringe, such as a pre-filled syringe. Using the approaches described herein, as well as variations of the same, movement of a stopper within a syringe can be directly and accurately assessed, and any risk of drug product contamination due to a breach in container closure integrity can also be assessed.

[0032] Fig. 1 is a front view of an exemplary drug delivery device, such as a syringe 10, in accordance with various embodiments of the present disclosure. The syringe 10 generally includes a syringe barrel 11 having a proximal open end 11a, a distal end 11b, a cavity 19, a flange portion 12, a plunger rod 16, and a stopper 18 (also referred to as “a plunger stopper”) movably disposed within the cavity 19 of the syringe barrel 11. The syringe barrel 11 also includes an inner annular wall 13 that defines the cavity 19 of the syringe barrel 11. The stopper 18 may be movably disposed within the cavity 19, and the stopper 18 may abut the inner annular wall 13 so as to form a fluid-tight relationship with the cavity 19 of the syringe 10. The syringe 10 may be a pre-filled syringe, and the syringe barrel 11 may be pre-filled with a drug or medicament.

[0033] The distal end 11b of the syringe barrel 11 may be configured to receive and/or support a needle or other suitable component for completing a fluid path into the patient. For example, the distal end 11b of the syringe barrel 11 may include a Luer lock component 17. In some embodiments, the Luer lock component 17 may be configured to receive a needle or other suitable component for completing a fluid path into the patient, such as a cannula. The open proximal end 11a of the syringe barrel 11 may be configured to receive the plunger rod 16 for pushing the stopper 18 in the distal direction towards the distal end 11b of the syringe barrel 11 and ejecting a fill volume 20 of drug or medicament from the cavity 19 of the syringe 10. For example, the stopper 18 may form a fluid-tight relationship with the cavity 19 of the syringe 10 while also being able to travel in

the distal direction along the cavity 19 and urge the fill volume 20 of drug from the distal end 11b of the syringe barrel 11. The fill volume 20 may refer to a volume of any liquid, such as a drug or a medicament, contained within the syringe barrel 11.

[0034] The plunger rod 16 may include a plunger rod end 14 with a larger diameter than the body portion of the plunger rod 16 to limit the travel distance of the plunger rod 16 in the distal direction and/or to make it easier for the user to depress the plunger rod 16. The stopper 18 may be a one-way component, and the plunger rod 16 may not be fixedly connected to the stopper 18, such that if the plunger rod 16 is moved in the proximal direction (opposite the distal direction), then the stopper 18 does not move with the plunger rod 16.

[0035] In some embodiments, the syringe barrel 11 may be made of plastic, glass, or any suitable material. As a more specific example, the syringe barrel 11 may be made of a plastic material including at least one or more of the following materials: certain grades of polypropylene (homo-polymer and/or co-polymer polypropylene), cyclo-olefin copolymer, cyclo-olefin polymer, cyclic olefin copolymer (COC), cyclo olefin polymer (COP), or other suitable materials. As a more specific example, the syringe barrel 11 may be made of cyclo olefin polymer (COP).

[0036] The flange 12 may include a diameter larger than that of the syringe barrel 11 and may serve as a finger rest permitting the user to manipulate the syringe 10 during use. For example, the user may rest two or more of her/his fingers against the flange 12 while using her/his thumb to depress the plunger rod end 14. The flange 12 may have a generally oval- or oblong-shaped configuration with a width 12a of approximately 13 millimeters, and the diameter of the syringe barrel 11 may be approximately 9.5 millimeters. Therefore, the flange 12 may have an effective grip surface of approximately 2 millimeters on each side of the flange 12.

[0037] The syringe barrel 11 may have a length of approximately 45 to 85 mm, approximately 60 to 65 mm, or another suitable length. The length of the syringe barrel 11 is the length between the proximal end 11a to the distal end 11b (but not including the needle, if present). The syringe barrel 11 may have an internal diameter of approximately 4 to 6.5 mm. If the syringe 10 has a nominal maximum fill volume 20 of approximately 1 ml, the internal diameter of the syringe barrel 11 may be approximately 5.5 to 6.5 mm. If the syringe 10 has a nominal maximum fill volume 20 of approximately 0.5 ml, the internal diameter of the syringe barrel 11 may be approximately 4 to 5 mm. In addition, the wall of the syringe barrel 11 may have a thickness of at least 1 mm; about 1 to 3 mm; about 1.5 to 3 mm; or about 2.4 to 2.8 mm.

[0038] In some embodiments, it may be desirable and/or required by regulations to externally sterilize an injection device, such as the syringe 10, during the manufacturing and/or assembly process. Additionally, some applications for pre-filled syringes (such as certain ophthalmic applications) require external sterilization. For example, 21 CFR 200.50 indicates, “Ophthalmic preparations and dispensers should be sterile.” Furthermore, ANSI/AAMI ST67:2011/(R)2017 states, “Sterilization of health care products - Requirements and guidance for selecting a sterility assurance level (SAL) for products labeled ‘sterile” and Section 4.1.1 – states: “Generally an SAL value of 10-6 has been used for terminal sterilization of health care products.” Furthermore, Annex A to the ST67 and EN556-1:2006 provide: “Sterilization of medical devices - Requirements for medical devices to be designated “STERILE” - Part 1: Requirements for terminally sterilized medical devices” . . . Section 4.1: “For a terminally-sterilized medical device to be designated "STERILE", the theoretical probability of there being a viable micro-organism present on/in the device shall be equal to or less than 1x10-6.” Therefore, it may be desirable and/or required for a bioburden to be less than 1x10-6 (e.g., 1 x 10^{-6}).

[0039] The terms “external sterilization” and/or “externally sterilize” as used herein refer to the process of sterilizing an injection device, such as the syringe 10, after it has been assembled. For example, the injection device may be externally sterilized after the syringe 10 (with a drug in the cavity 19), plunger rod 16, stopper 18, and protective cap (not shown) have all been assembled and packaged in a blister tray with a breathable lid that acts as a sterile barrier while allowing for gas flow and airflow (such as sterilant gas). During the external sterilization process, the syringe 10 may be placed in a sterilization chamber and exposed to a sterilization gas, such as Ethylene Oxide (EtO), Nitrogen Dioxide (NO2), Vaporized Hydrogen Peroxide (VHP),

Carbon Dioxide (CO_2), chlorine dioxide, or any other suitable gas, for a predetermined length of time and other specified conditions (such as temperature and pressure). Then, after the sterilization cycle, the sterilization gas is purged from the chamber and the injection device remains in the chamber (which is substantially or completely free of sterilization gas) for another predetermined length of time and other specified conditions (such as temperature and pressure). The external sterilization process may also include a drying phase prior to the sterilant injection and an aeration phase after the sterilant removal in which, for each type of phase, several vacuum pressures are applied and released as pressure evacuations and injections as intended to remove chamber humidity or to remove sterilant gas from the load and chamber, respectively. The external sterilization process may also include a humidification phase just prior to the injection of the sterilant gas, in which humid air is injected into the sterilization chamber in one or more pulses. The external sterilization process may also include multiple sets of phases inclusive of the sterilant gas injection and dwell phase in which each set of these phases may comprise a sterilant pulse.

[0040] For example, in order to assemble and externally sterilize the syringe 10, according to various embodiments of the present disclosure, at least some individual components of the syringe 10 may be sterilized first, often prior to receipt by the manufacturing facility. By way of example, the syringe barrel 11 and the stopper 18, and any other components that may have direct contact with a drug product or medicament, may be sterilized during the initial step. This step may utilize a variety of known techniques for sterilizing various unassembled components of the drug delivery device. Afterwards, the syringe barrel 11 may be filled with a drug product or medicament, and the stopper 18 may be assembled or movably disposed within the syringe barrel 11. The assembly step may also include adding at least some of the following: a plunger rod 16, a tip cap with Luer Lock 17, a needle, a rigid needle shield, and/or a protective cap. At least some of these components may be pre-assembled with each other, but they may also be assembled at the filling line, such as if the filling process is performed aseptically. Afterwards, at the manufacturing site or the assembling site, the assembled syringe 10 may be placed into a packaging, such as a secondary packaging. Next, the packaged syringe 10 may be externally sterilized. The external sterilization steps may be performed on the syringe 10 while the assembled syringe 10 is supported by the packaging and contained within the packaging.

[0041] To externally sterilize the syringe 10, in some embodiments, the syringe 10 may need to be preconditioned. For a process utilizing Nitrogen Dioxide (NO_2), preconditioning may include at least some or all of the following steps: removing the syringe 10 from storage, allowing the syringe 10 to adjust to room condition equilibration for a desired amount of time (such as 30 minutes, 90 minutes, 2 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, or any desirable amount of time), and placing the syringe 10 into a sterilization chamber. Preconditioning may occur inside or outside of the sterilization chamber.

[0042] When utilizing Ethylene Oxide (EtO), the precondition step may vary slightly than the step described for NO_2. For example, the syringe 10 may be preconditioned inside of the sterilization chamber (without gas injection) for 360 minutes (or another desirable length of time). However, as with the process utilizing NO_2, the preconditioning step utilizing EtO may occur inside or outside of the sterilization chamber. Moreover, while the aeration step is typically performed in the sterilization chamber, when utilizing EtO, the aeration step may be performed outside of the sterilization chamber.

[0043] Next, the sterilization chamber may be closed and all or substantially all of the air may be evacuated from the sterilization chamber. Next, the sterilization chamber may be humidified to a desired setting, such as 75 or 80 (or any desired amount of percentage of relative humidity). Next, the desired sterilization gas (also referred to as “sterilant gas”) may be injected into the sterilization chamber and held in the sterilization chamber for a desired dwell time. For recipes utilizing NO_2, the sterilant gas injection step may include some or all of the following steps: delivering a dose of NO_2 by pulling a vacuum in the sterilization chamber for a desired amount of time (i.e., dwell time) while injecting a desired amount of sterilant gas (dose concentration), purging the sterilant gas and releasing the vacuum, and then repeating these steps for a desired number of pulses. Once the number of desired pulses is complete, the sterilant gas may then be finally purged so that the sterilant gas is removed from the sterilization chamber. Finally, the sterilization chamber may be aerated for a desired number of cycles to ensure that all or

substantially all of the sterilization gas has been flushed from the syringe 10. In some examples, the vacuum level may vary during these steps; for example the vacuum during dwell time may be minimal, such as approximately 590 Torr.

[0044] The external sterilization method described above may include any suitable parameters, such as:

- The vacuum level may be between about 100 and 500 Torr, between about 150 and 400 Torr, between about 150 and 300 Torr, or another suitable vacuum level.
- The concentration of the dose of the NO2 may be between about 2 and 20 milligrams per Liter, between about 2 and 10 milligrams per Liter, between about 2 and 7 milligrams per Liter, or another suitable concentration of the dose.
- The chamber may have a relative humidity of between about 70 and 90 percent or another suitable humidity.
- The dwell time may be between about 2 and 20 minutes, between about 2 and 12 minutes, between about 2 and 7 minutes, or another suitable dwell time.
- The number of pulses may be between about 1 and 24, between about 1 and 12, between about 1 and 8, between about 1 and 4, between about 1 and 2, or another suitable number of pulses.
- The step of aerating the sterilization chamber may include aerating the sterilization chamber a number of cycles between about 100 and 400, between about 150 and 350, or another suitable number of cycles.

[0045] However, during the external sterilization process described above, one or more individual components of the injection device, such as the stopper 18 of the syringe 10, may be prone to move within the syringe barrel 11, for example, due to pressure changes in the sterilization chamber. In addition, when the syringe 10 is shipped to a manufacturing facility or when the syringe 10 is assembled at the filling line, one or more individual components of the syringe 10, such as the stopper 18 movably disposed within the syringe barrel 11, may be prone to move in response to various shipping and handling conditions. Finally, when individual components, such as the plunge rod 16, are being individually manufactured and assembled in the syringe 10, the stopper 18 may move during the manufacturing and assembly process.

[0046] Any movement of the stopper 18 in the syringe 10 may pose a risk of potential drug product contamination due to the fill volume of drug or medicament contained within the cavity 19 coming into contact with a non-sterile surface of the syringe barrel 11. Fig. 2 illustrates an exploded front view of the syringe barrel 11 of the syringe 10, according to various embodiments of the present disclosure. As shown in Fig. 2, the stopper 18 includes a body portion 203 having a generally cylindrical sidewall and a plurality of ribs 202a, 202b projecting radially outwardly from the sidewall of the body portion 203. The first rib 202a may project radially outwardly from the sidewall of the body portion 203 near the proximal face 201 of the stopper 18, and the second rib 202b may project radially outwardly from the sidewall of the body portion 203 near the distal face 204 of the stopper 18. As used herein, the “proximal face” of the stopper refers to the side of stopper that is opposite to and not in contact with the fill volume, and the “distal face” of the stopper refers to the side of the stopper that is in contact with the fill volume. The sidewalls of the ribs 202a, 202b may abut the inner annular wall 13 of the syringe barrel 11 around the entire diameter of the inner annular wall 13. Accordingly, the ribs 202a, 202b may be configured to form a fluid-tight relationship between the stopper 18 and the cavity 19 of the syringe barrel 11 such that the fill volume 20 of drug or medicament below the distal face 204 of the stopper 18 cannot travel in the proximal direction past the distal face 204 of the stopper 18. Although Fig. 2 illustrates a stopper 18 having two ribs 202a, 202b, the stopper 18 may have any number of ribs projecting radially outwardly from the sidewall of the body portion 203 and forming a fluid-tight relationship with the cavity 19. For example, the stopper 18 may have one rib, three ribs, four ribs, five ribs, or six ribs. In other embodiments, the stopper 18 may have no ribs.

[0047] In some embodiments, as shown in Figs. 2-5, the proximal face 201 of the stopper 18 may further include a convex surface 220. The convex surface 220 may be configured to allow for gravity to pull any inoculated biological particulate or liquid inoculum towards the outer perimeter of the rib 202a and ensure that the inoculated biological particulate covers the interface between the rib 202a of the stopper 18 and the inner annular wall 13 of the syringe barrel 11. Thus, the convex surface 220 may

allow for gravity to assist in ensuring the inoculated biological particulate is present at the interface of the edges of the rib 202a and the inner annular wall 13 of the syringe barrel 11.

[0048] Referring to Fig. 2, for example, if the amount of movement of the stopper 18 in the proximal direction (towards the proximal end 11a of the syringe barrel 11) is equal to or exceeds the axial length between the proximal face 201 of the stopper 18 and the distal face 204 of the stopper 18 (i.e., "sterile barrier height" in Fig. 2), a breach in container closure integrity (CCI) may occur. That is, due to the fill volume 20 of drug or medicament contained within the sterile zone of the cavity 19 of the syringe barrel 11 coming into contact with the non-sterile zone of the syringe barrel 11, there may be a risk of potential drug product contamination. Therefore, prior to assembling and externally sterilizing a syringe, it may be critical to assess whether any stopper movement would occur during shipping, handling, manufacturing, or assembly processes, as well as during any external sterilization process, to ensure any drug product contained within the syringe would not be contaminated. As used herein, the "sterile barrier height" of the stopper may refer to the distance between (a) the most proximal surface of the stopper in contact with the inner wall of the syringe barrel 11 and (b) the most distal surface of the stopper in contact with the inner wall of the syringe barrel 11. In Fig. 2, for example, the sterile barrier height refers to the distance between the proximal end of the proximal face 201 of the stopper 18 in contact with the inner wall of the syringe barrel 11 and the distal end of the distal face 204 in contact with the inner wall of the syringe barrel 11.

[0049] As discussed above, methods for indirectly analyzing the risk of drug product contamination due to stopper movement and related container closure integrity breach issues exist. For example, conventional approaches, such as charcoal powder displacement test, microbial ingress test, dye ingress test, and mass extraction test, indirectly assess stopper movement primarily based on measuring the final distance traveled by the stopper under simulated conditions. Because conventional assessments are performed under simulated conditions, various assumptions made and theoretical worst-case conditions used for syringe configuration not only create ambiguity in the assessment, but also fail to provide an accurate assessment of stopper movement and risk of drug product contamination in syringes. The present disclosure describes approaches embodying advantageous alternatives to these conventional methods, and that may address one or more of the challenges or needs mentioned herein, as well as provide other benefits and advantages.

[0050] By way of example, Fig. 8 illustrates a method 800 of assessing stopper movement in a syringe by direct inoculation of a biological particulate into the syringe barrel and onto the proximal face of the stopper, according to various embodiments of the present disclosure. The method 800 will be described with reference to Figs. 3-5, each of which illustrate an exploded front view of the syringe barrel 11 of the syringe 10 with the stopper 18 movably disposed within the cavity 19 of the syringe barrel 11, according to various embodiments of the present disclosure. The cavity 19 may contain a fill volume 20 of liquid, such as a drug or medicament. In other embodiments, the cavity 19 may contain a fill volume 20 of testing solution, instead of a drug or medicament.

[0051] Referring to Figs. 3-5 and 8, the method 800 of assessing movement of the stopper 18 in the syringe 10 begins at step 802. At step 802, a biological particulate 300 is directly inoculated through the open, proximal end 11a (shown in Fig. 1) of the syringe barrel 11 and onto the proximal face 201 of the stopper 18. The biological particulate 300 is inoculated such that the biological particulate 300 covers at least a portion of an interface between the proximal face 201 of the first rib 202a of the stopper 18 and the inner annular wall 13 of the syringe barrel 11. Accordingly, this method of assessing stopper movement will ensure that the biological particulate 300 is inoculated at the precise location of the non-sterile zone (shown in Fig. 2) that would first come into contact with the fill volume 20 of drug or medicament should the stopper 18 move past the sterile barrier height during the process(es) of interest.

[0052] As shown in Fig. 3, the biological particulate 300 may be directly inoculated onto the proximal face 201 of the stopper 18 such that the biological particulate 300 covers (1) the entire proximal face 201, and (2) the interface between the proximal face 201 of the first rib 202a and the inner annular wall 13 of the syringe barrel 11. In other embodiments, as shown in Fig. 4, the

biological particulate 300 may be directly inoculated across the interface between the proximal face 201 and the inner annular wall 13 of the syringe barrel 11 in one streak. This streaking method may minimize resistance to stopper movement that may be added due to the inoculation of the biological particulate 300. Although Fig. 4 illustrates inoculating the biological particulate 300 in one streak, the biological particulate 300 may be inoculated in any number of individual streaks. In yet another embodiment, as shown in Fig. 5, the biological particulate 300 may be directly inoculated at the interface between the proximal face 201 and the inner annular wall 13 of the syringe barrel 11 in one stamp, using a wand with foam or sponge-like tip that is contoured to fit the shape of the interface. The biological particulate 300 may be inoculated at one or more locations around the diameter of the proximal face 201 of the stopper 18. For example, as shown in Fig. 4, the biological particulate 300 may be inoculated at one location around the diameter of the proximal face 201 along the interface between the proximal face 201 and the inner annular wall 13. Alternatively, as shown in Fig. 5, the biological particulate 300 may be inoculated at a plurality of locations around the diameter of the proximal face 201 along the interface between the proximal face 201 and the inner annular wall 13.

[0053] In some embodiments, the biological particulate 300 be a liquid inoculum comprising at least one of: a microorganism, a fungus, a bacterium, a spore, a virus, a biological cell, a biological antigen, a protein, or a protein antigen. For example, the biological particulate 300 may comprise approximately 10^5 or 10^5 CFU/ mL of bacterial spore suspension.

[0054] Referring back to Fig. 8, once the syringe barrel 11 is inoculated with the biological particulate 300, at step 804, the inoculated syringe 10 may be subjected to one or more conditions. That is, at step 804, one or more actual process(es) of interest may be executed with the inoculated syringe 10. By way of example, the inoculated syringe 10 may be subjected to an actual external sterilization process described above, an actual manufacturing process, an actual syringe assembly process, actual shipping and handling conditions during manufacturing, assembly, and/or transport, and/or any combination thereof. Additionally, or alternatively, the inoculated syringe 10 may be subjected to nominal or adjusted parameters and testing conditions for one or more actual process(es) of interest. The parameters and testing conditions may be selected to ensure that the assessment is challenging the syringe 10 for stopper movement under conditions that are at or beyond the upper or lower parameter limits (i.e., to increase stopper movement beyond what normally occurs at nominal parameters) for the process(es) of interest.

[0055] After subjecting the syringe 10 to one or more conditions, the method 800 may proceed to step 806, at which the fill volume 20 of liquid is extracted from the cavity 19 of the syringe 10. In some embodiments, the fill volume 20 of liquid may have previously been verified to be sterile prior to step 804. At step 808, a sterility test on the extracted fill volume 20 of liquid may be performed. In particular, the extracted fill volume 20 of liquid may be suspended into a testing medium. In some embodiments, the testing medium may contain Trypticase Soy Broth (TSB) or Fluid Thioglycollate Medium (FTM). The testing medium may become turbid if there is any presence of a surviving biological particulate 300 within the extracted fill volume 20 of liquid. Accordingly, if the testing medium becomes turbid once the extracted fill volume 20 of liquid is suspended therein, this may be indicative of a positive growth result (i.e., a presence of the biological particulate 300 within the extracted fill volume 20 of liquid) and, thus, be indicative of movement of the stopper 18 in the syringe 10 beyond the stopper's sterile barrier height and a potential risk of drug product contamination during the actual process(es). On the other hand, if the sterility test yields negative growth results and the testing medium does not become turbid once the extracted fill volume 20 of liquid is suspended therein, this may indicate that any movement of the stopper 18 did not exceed beyond the stopper's sterile barrier height and no risk of drug product contamination was identified during the actual process(es). Therefore, at step 810, whether any movement of the stopper 18 in the syringe 10 exceeded its sterile barrier height to cause drug product contamination may be determined based on the sterility test performed. In some embodiments, instead of suspending the extracted fill volume 20 into the testing medium, the fill volume 20 may already comprise the testing medium, such as TSB or FTM. Accordingly, after extracting the fill volume 20 of liquid at step 806, a sterility test can be directly performed on the extracted fill volume 20 at step 808 without having to suspend the extracted fill volume 20 in the testing medium first.

[0056] Fig. 9 illustrates a method 900 of determining a risk of drug product contamination in a syringe, according to various embodiments of the present disclosure. Similar to the method 800, the method 900 begins at step 902, at which the biological particulate 300 is directly inoculated through the open, proximal end 11a (shown in Fig. 1) of the syringe barrel 11 and onto the proximal face 201 of the stopper 18. Once the syringe barrel 11 is inoculated with the biological particulate 300, at step 904, the inoculated syringe 10 may be subjected to one or more conditions. Similar to step 804, at step 904, one or more actual process(es) of interest may be executed with the inoculated syringe 10. By way of example, the inoculated syringe 10 may be subjected to an actual external sterilization process described above, an actual manufacturing process, an actual syringe assembly process, actual shipping and handling conditions during manufacturing, assembly, and/or transport, and/or any combination thereof. Additionally, or alternatively, the inoculated syringe 10 may be subjected to nominal or adjusted parameters and testing conditions for one or more actual process(es) of interest. The parameters and testing conditions may be selected to ensure that the assessment is challenging the syringe 10 for stopper movement under conditions that are at or beyond the upper or lower parameter limits (i.e., to increase stopper movement beyond what normally occurs at nominal parameters) for the process(es) of interest.

[0057] After subjecting the syringe 10 to one or more conditions, the method 900 may proceed to step 906, at which the fill volume 20 of liquid is extracted from the cavity 19 of the syringe 10. In some embodiments, the fill volume 20 of liquid may have previously been verified to be sterile prior to step 904. At step 908, a sterility test on the extracted fill volume 20 of liquid may be performed. In particular, the extracted fill volume 20 of liquid may be suspended into a testing medium. In some embodiments, the testing medium may contain Trypticase Soy Broth (TSB) or Fluid Thioglycollate Medium (FTM). The testing medium may become turbid if there is any presence of a surviving biological particulate 300 within the extracted fill volume 20 of liquid. Accordingly, if the testing medium becomes turbid once the extracted fill volume 20 of liquid is suspended therein, this may be indicative of a positive growth result (i.e., a presence of the biological particulate 300 within the extracted fill volume 20 of liquid) and, thus, be indicative of movement of the stopper 18 in the syringe 10 beyond the stopper's sterile barrier height and a potential risk of drug product contamination during the actual process(es). On the other hand, if the sterility test yields negative growth results and the testing medium does not become turbid once the extracted fill volume 20 of liquid is suspended therein, this may indicate that any movement of the stopper 18 did not exceed beyond the stopper's sterile barrier height and no risk of drug product contamination was identified during the actual process(es). Therefore, at step 910, whether any movement of the stopper 18 in the syringe 10 exceeded its sterile barrier height to cause drug product contamination may be determined based on the sterility test performed.

[0058] The method 900 may then proceed to step 912, at which any risk of drug product contamination is identified or determined based at least one the stopper movement determined at step 910. For example, if the distance moved by the stopper 18 in the proximal direction within the syringe barrel 11 is equal to or exceeds the sterile barrier height of the stopper 18 (i.e., the axial length between the proximal face 201 and the distal face 204 of the stopper 18), then a risk of drug product contamination may exist due to the fill volume of drug or medicament contained within the cavity 19 coming into contact with the non-sterile surface or non-sterile zone of the syringe barrel 11. On the other hand, if the distance moved by the stopper 18 in the proximal direction within the syringe barrel 11 is less than the sterile barrier height of the stopper 18, a risk of drug product contamination may not exist.

[0059] The methods of assessing stopper movement in a syringe and identifying stopper movement exceeding the sterile barrier height of the stopper resulting in a risk of drug product contamination according to the present disclosure may have one or more advantages relative to conventional approaches, any one or more of which may be present in a particular embodiment in accordance with the features of the present disclosure included in that embodiment. For example, the methods according to the present disclosure provide a direct assessment of stopper movement and drug product contamination utilizing the actual process(es) of interest, such as an actual external sterilization process described above, an actual manufacturing process, an

actual syringe assembly process, actual shipping and handling conditions during manufacturing, assembly, and/or transport, and/or any combination thereof. Accordingly, because the assessment and sterility test performed are not done under simulated conditions, no assumptions need to be made that could introduce ambiguity and subjectivity in the final analysis and results. In addition, the methods according to the present disclosure uses a microbiological approach to perform the sterility test on the extracted fill volume of liquid, thereby providing an accurate measurement of stopper movement and potential drug product contamination. Moreover, for assessment of stopper movement due to an external sterilization process, in some situations, the syringe may be subject to pressure changes that occur at the end or towards the end of the external sterilization cycle that causes stopper movement to exceed the stopper's sterile barrier height, but only after external surface sterility or lethality has already been achieved for the syringe during the initial portion of the sterilization cycle. Accordingly, even if the stopper movement exceeded the sterile barrier height, there may be no risk of drug product contamination because the drug product would only come into contact with sterile surfaces. The methods according to the present disclosure may provide verification that no drug product contamination occurred using the external sterilization process, despite the stopper movement exceeding the sterile barrier height at the end of the external sterilization process, since the inner annular walls and any external surfaces beyond the sterile zone of the syringe were sterilized prior to the stopper movement. Other advantages not specifically listed herein may also be recognized as well.

[0060] Referring now to Figs. 6A, 6B, 7A, and 7B, exemplary embodiments of a plunger rod and a stopper are shown, according to various embodiments of the present disclosure. As shown in Figs. 6A and 6B, in some embodiments, a stopper 618 may include a body portion 603 having a generally cylindrical sidewall and a plurality of ribs 602a, 602b projecting radially outwardly from the sidewall of the body portion 603. The first rib 602a may project radially outwardly from the sidewall of the body portion 603 near the proximal end of the stopper 618, and the second rib 602b may project radially outwardly from the sidewall of the body portion 603 near the distal end of the stopper 618. Although Figs. 6A and 6B illustrate the stopper 618 having two ribs 602a, 602b, the stopper 618 may have any number of ribs projecting radially outwardly from the sidewall of the body portion 603. For example, the stopper 618 may have one rib, three ribs, four ribs, five ribs, or six ribs. In alternative embodiments, the stopper 618 may have no ribs. Accordingly, the sterile barrier height for the stopper with no ribs may be defined as the distance between (a) the most proximal surface of the stopper in contact with the inner wall of the syringe barrel 11 and (b) the most distal surface of the stopper in contact with the inner wall of the syringe barrel 11.

[0061] In some embodiments, as shown in Figs. 6A and 6B, the stopper 618 may have a proximal face 601, and the proximal face 601 may include a convex surface. The convex proximal face 601 may be configured to allow for gravity to pull any inoculated biological particulate or liquid inoculum towards the outer perimeter of the first rib 602a and ensure that the inoculated biological particulate covers the interface between the first rib 602a of the stopper 618 and the inner annular wall 13 of the syringe barrel 11 (shown in Figs. 1-5). Because the proximal face 601 of the stopper 618 includes a convex surface, the plunger rod 616 may include a concave distal tip 615 to complement the convex proximal face 601 of the stopper 618.

[0062] In other embodiments, as shown in Figs. 7A and 7B, a stopper 718 may include a body portion 703 having a generally cylindrical sidewall and a plurality of ribs 702a, 702b projecting radially outwardly from the sidewall of the body portion 703. The first rib 702a may project radially outwardly from the sidewall of the body portion 703 near the proximal end of the stopper 718, and the second rib 702b may project radially outwardly from the sidewall of the body portion 703 near the distal end of the stopper 718. Although Figs. 7A and 7B illustrate the stopper 718 having two ribs 702a, 702b, the stopper 718 may have any number of ribs projecting radially outwardly from the sidewall of the body portion 703. For example, the stopper 718 may have one rib, three ribs, four ribs, five ribs, or six ribs.

[0063] Similar to the stopper 618 in Figs. 6A and 6B, the stopper 718 may have a convex proximal face 701. The convex proximal face 701 may be configured to allow for gravity to pull any inoculated biological particulate or liquid inoculum towards the outer perimeter of the first rib 702a and ensure that the inoculated biological particulate covers the interface between the first

rib 702a of the stopper 718 and the inner annular wall 13 of the syringe barrel 11 (shown in Figs. 1-5). Because the proximal face 701 of the stopper 718 includes a convex surface, the plunger rod 716 may include a generally concave distal tip 715 to complement the convex proximal face 701 of the stopper 718.

[0064] Additionally, or alternatively, the stopper 718 may include a plurality of protrusions 705 protruding axially upwards from the proximal face 701 of the stopper 718. Although Figs. 7A and 7B illustrate the stopper 718 having four protrusions 705 on the proximal face 701, the proximal face 701 may include any number of protrusions. For example, the proximal face 701 may have one protrusion, two protrusions, three protrusions, five protrusions, or six protrusions. The protrusions 705 may be configured to reduce contact surfaces between the proximal face 701 of the stopper 718 and the concave distal tip 715 of the plunger rod 716. In some embodiments, the distal tip 715 of the plunger rod 716 may also include one or more protrusion(s) 717 configured to reduce contact surfaces between the proximal face 701 of the stopper 718 and the concave distal tip 715 of the plunger rod 716. Reducing contact surfaces between the stopper 718 and the plunger rod 716 may optimize sterilant gas flow during the above-described external sterilization process and minimize occlusion.

[0065] The above description describes various devices, assemblies, components, subsystems and methods for use related to a drug delivery device. The devices, assemblies, components, subsystems, methods or drug delivery devices can further comprise or be used with a drug including but not limited to those drugs identified below as well as their generic and biosimilar counterparts. The term drug, as used herein, can be used interchangeably with other similar terms and can be used to refer to any type of medicament or therapeutic material including traditional and non-traditional pharmaceuticals, nutraceuticals, supplements, biologics, biologically active agents and compositions, large molecules, biosimilars, bioequivalents, therapeutic antibodies, polypeptides, proteins, small molecules and generics. Non-therapeutic injectable materials are also encompassed. The drug may be in liquid form, a lyophilized form, or in a reconstituted from lyophilized form. The following example list of drugs should not be considered as all-inclusive or limiting.

[0066] The drug will be contained in a reservoir. In some instances, the reservoir is a pre-filled syringe. The pre-filled syringe may have a maximum fill volume, i.e. a volume which can be maximally taken up by the syringe, of 0.3 ml to 1.5ml, preferably of 0.5 ml to 1.0 ml. The volume of the liquid composition filled into the syringe may be about 0.05 ml to 1.0 ml; about 0.1 ml to 0.5 ml; about 0.14 ml to 0.3 ml; or about 0.15 ml to 0.2 ml. Syringes are typically filled with a larger volume than the volume actually administered to the patient to take into account any dead space within the syringe and the needle and the loss due to the preparation of the syringe for injection. Therefore, the volume which is actually administered to the patient may be between 0.01 ml and 1 ml; between 0.02 and 0.5 ml; between 0.025 and 0.5 ml; between 0.03 ml and 0.05 ml; or 0.05 ml.

[0067] In some embodiments, the reservoir of the pre-filled syringe includes a VEGF antagonist. The term "VEGF antagonist" refers to a molecule which specifically interacts with VEGF and inhibits one or more of its biological activities, e.g. its mitogenic, angiogenic and/or vascular permeability activity. It is intended to include both anti-VEGF antibodies and antigen-binding fragments thereof and non-antibody VEGF antagonists. Non-antibody VEGF antagonists include aflibercept, pegaptanib and antibody mimetics. Preferably, the non-antibody VEGF antagonist is aflibercept. Aflibercept which is presently marketed under the name Eylea® and which is also known as VEGF-trap is a recombinant human soluble VEGF receptor fusion protein in which portions of human VEGF receptors 1 and 2 extracellular domains are fused to the Fc portion of human IgGl (Holash et al. (2002) Proc. Natl. Acad. Sci. USA 99(17): 11393-11398; WO 00/75319 Al).

[0068] In some embodiments, the reservoir of the drug delivery device may be filled with or the device can be used with colony stimulating factors, such as granulocyte colony-stimulating factor (G-CSF). Such G-CSF agents include but are not limited to Neulasta® (pegfilgrastim, pegylated filgastrim, pegylated G-CSF, pegylated hu-Met-G-CSF) and Neupogen® (filgrastim, G-CSF, hu-MetG-CSF), UDENYCA® (pegfilgrastim-cbqv), Ziextenzo® (LA-EP2006; pegfilgrastim-bmez), or FULPHILA (pegfilgrastim-bmez).

[0069] In other embodiments, the drug delivery device may contain or be used with an erythropoiesis stimulating agent (ESA), which may be in liquid or lyophilized form. An ESA is any molecule that stimulates erythropoiesis. In some embodiments, an ESA is an erythropoiesis stimulating protein. As used herein, "erythropoiesis stimulating protein" means any protein that directly or indirectly causes activation of the erythropoietin receptor, for example, by binding to and causing dimerization of the receptor. Erythropoiesis stimulating proteins include erythropoietin and variants, analogs, or derivatives thereof that bind to and activate erythropoietin receptor; antibodies that bind to erythropoietin receptor and activate the receptor; or peptides that bind to and activate erythropoietin receptor. Erythropoiesis stimulating proteins include, but are not limited to, Epogen® (epoetin alfa), Aranesp® (darbepoetin alfa), Dynepo® (epoetin delta), Mircera® (methyoxy polyethylene glycol-epoetin beta), Hematide®, MRK-2578, INS-22, Retacrit® (epoetin zeta), Neorecormon® (epoetin beta), Silapo® (epoetin zeta), Binocrit® (epoetin alfa), epoetin alfa Hexal, Abseamed® (epoetin alfa), Ratioepo® (epoetin theta), Eporatio® (epoetin theta), Biopoin® (epoetin theta), epoetin alfa, epoetin beta, epoetin iota, epoetin omega, epoetin delta, epoetin zeta, epoetin theta, and epoetin delta, pegylated erythropoietin, carbamylated erythropoietin, as well as the molecules or variants or analogs thereof.

[0070] Among particular illustrative proteins are the specific proteins set forth below, including fusions, fragments, analogs, variants or derivatives thereof: OPGL specific antibodies, peptibodies, related proteins, and the like (also referred to as RANKL specific antibodies, peptibodies and the like), including fully humanized and human OPGL specific antibodies, particularly fully humanized monoclonal antibodies; Myostatin binding proteins, peptibodies, related proteins, and the like, including myostatin specific peptibodies; IL-4 receptor specific antibodies, peptibodies, related proteins, and the like, particularly those that inhibit activities mediated by binding of IL-4 and/or IL-13 to the receptor; Interleukin 1-receptor 1 ("IL1-R1") specific antibodies, peptibodies, related proteins, and the like; Ang2 specific antibodies, peptibodies, related proteins, and the like; NGF specific antibodies, peptibodies, related proteins, and the like; CD22 specific antibodies, peptibodies, related proteins, and the like, particularly human CD22 specific antibodies, such as but not limited to humanized and fully human antibodies, including but not limited to humanized and fully human monoclonal antibodies, particularly including but not limited to human CD22 specific IgG antibodies, such as, a dimer of a human-mouse monoclonal hLL2 gamma-chain disulfide linked to a human-mouse monoclonal hLL2 kappa-chain, for example, the human CD22 specific fully humanized antibody in Epratuzumab, CAS registry number 501423-23-0; IGF-1 receptor specific antibodies, peptibodies, and related proteins, and the like including but not limited to anti-IGF-1R antibodies; B-7 related protein 1 specific antibodies, peptibodies, related proteins and the like ("B7RP-1" and also referring to B7H2, ICOSL, B7h, and CD275), including but not limited to B7RP-specific fully human monoclonal IgG2 antibodies, including but not limited to fully human IgG2 monoclonal antibody that binds an epitope in the first immunoglobulin-like domain of B7RP-1, including but not limited to those that inhibit the interaction of B7RP-1 with its natural receptor, ICOS, on activated T cells; IL-15 specific antibodies, peptibodies, related proteins, and the like, such as, in particular, humanized monoclonal antibodies, including but not limited to HuMax IL-15 antibodies and related proteins, such as, for instance, 145c7; IFN gamma specific antibodies, peptibodies, related proteins and the like, including but not limited to human IFN gamma specific antibodies, and including but not limited to fully human anti-IFN gamma antibodies; TALL-1 specific antibodies, peptibodies, related proteins, and the like, and other TALL specific binding proteins; Parathyroid hormone ("PTH") specific antibodies, peptibodies, related proteins, and the like; Thrombopoietin receptor ("TPO-R") specific antibodies, peptibodies, related proteins, and the like;Hepatocyte growth factor ("HGF") specific antibodies, peptibodies, related proteins, and the like, including those that target the HGF/SF:cMet axis (HGF/SF:c-Met), such as fully human monoclonal antibodies that neutralize hepatocyte growth factor/scatter (HGF/SF); TRAIL-R2 specific antibodies, peptibodies, related proteins and the like; Activin A specific antibodies, peptibodies, proteins, and the like; TGF-beta specific antibodies, peptibodies, related proteins, and the like; Amyloid-beta protein specific antibodies, peptibodies, related proteins, and the like; c-Kit specific antibodies, peptibodies, related proteins, and the like, including but not limited to proteins that bind c-Kit and/or other stem cell factor receptors; OX40L specific antibodies, peptibodies, related proteins, and the like, including but not limited to proteins that bind OX40L and/or other ligands of the OX40 receptor;

Activase® (alteplase, tPA); Aranesp® (darbepoetin alfa) Erythropoietin [30-asparagine, 32-threonine, 87-valine, 88-asparagine, 90-threonine], Darbepoetin alfa, novel erythropoiesis stimulating protein (NESP); Epogen® (epoetin alfa, or erythropoietin); GLP-1, Avonex® (interferon beta-1a); Bexxar® (tositumomab, anti-CD22 monoclonal antibody); Betaseron® (interferon-beta); Campath® (alemtuzumab, anti-CD52 monoclonal antibody); Dynepo® (epoetin delta); Velcade® (bortezomib); MLN0002 (anti-α4ß7 mAb); MLN1202 (anti-CCR2 chemokine receptor mAb); Enbrel® (etanercept, TNF-receptor /Fc fusion protein, TNF blocker); Eprex® (epoetin alfa); Erbitux® (cetuximab, anti-EGFR / HER1 / c-ErbB-1); Genotropin® (somatropin, Human Growth Hormone); Herceptin® (trastuzumab, anti-HER2/neu (erbB2) receptor mAb); Kanjinti™ (trastuzumab-anns) anti-HER2 monoclonal antibody, biosimilar to Herceptin®, or another product containing trastuzumab for the treatment of breast or gastric cancers; Humatrope® (somatropin, Human Growth Hormone); Humira® (adalimumab); Vectibix® (panitumumab), Xgeva® (denosumab), Prolia® (denosumab), Immunoglobulin G2 Human Monoclonal Antibody to RANK Ligand, Enbrel® (etanercept, TNF-receptor /Fc fusion protein, TNF blocker), Nplate® (romiplostim), rilotumumab, ganitumab, conatumumab, brodalumab, insulin in solution; Infergen® (interferon alfacon-1); Natrecor® (nesiritide; recombinant human B-type natriuretic peptide (hBNP); Kineret® (anakinra); Leukine® (sargamostim, rhuGM-CSF); LymphoCide® (epratuzumab, anti-CD22 mAb); Benlysta™ (lymphostat B, belimumab, anti-BlyS mAb); Metalyse® (tenecteplase, t-PA analog); Mircera® (methoxy polyethylene glycol-epoetin beta); Mylotarg® (gemtuzumab ozogamicin); Raptiva® (efalizumab); Cimzia® (certolizumab pegol, CDP 870); Soliris™ (eculizumab); pexelizumab (anti-C5 complement); Numax® (MEDI-524); Lucentis® (ranibizumab); Panorex® (17-1A, edrecolomab); Trabio® (lerdelimumab); TheraCim hR3 (nimotuzumab); Omnitarg (pertuzumab, 2C4); Osidem® (IDM-1); OvaRex® (B43.13); Nuvion® (visilizumab); cantuzumab mertansine (huC242-DM1); NeoRecormon® (epoetin beta); Neumega® (oprelvekin, human interleukin-11); Orthoclone OKT3® (muromonab-CD3, anti-CD3 monoclonal antibody); Procrit® (epoetin alfa); Remicade® (infliximab, anti-TNFα monoclonal antibody); Reopro® (abciximab, anti-GP IIb/IIia receptor monoclonal antibody); Actemra® (anti-IL6 Receptor mAb); Avastin® (bevacizumab), HuMax-CD4 (zanolimumab); Mvasi™ (bevacizumab-awwb); Rituxan® (rituximab, anti-CD20 mAb); Tarceva® (erlotinib); Roferon-A®-(interferon alfa-2a); Simulect® (basiliximab); Prexige® (lumiracoxib); Synagis® (palivizumab); 145c7-CHO (anti-IL15 antibody, see U.S. Patent No. 7,153,507); Tysabri® (natalizumab, anti-α4integrin mAb); Valortim® (MDX-1303, anti-B. anthracis protective antigen mAb); ABthrax™; Xolair® (omalizumab); ETI211 (anti-MRSA mAb); IL-1 trap (the Fc portion of human IgG1 and the extracellular domains of both IL-1 receptor components (the Type I receptor and receptor accessory protein)); VEGF trap (Ig domains of VEGFR1 fused to IgG1 Fc); Zenapax® (daclizumab); Zenapax® (daclizumab, anti-IL-2Rα mAb); Zevalin® (ibritumomab tiuxetan); Zetia® (ezetimibe); Orencia® (atacicept, TACI-Ig); anti-CD80 monoclonal antibody (galiximab); anti-CD23 mAb (lumiliximab); BR2-Fc (huBR3 / huFc fusion protein, soluble BAFF antagonist); CNTO 148 (golimumab, anti-TNFα mAb); HGS-ETR1 (mapatumumab; human anti-TRAIL Receptor-1 mAb); HuMax-CD20 (ocrelizumab, anti-CD20 human mAb); HuMax-EGFR (zalutumumab); M200 (volociximab, anti-α5β1 integrin mAb); MDX-010 (ipilimumab, anti-CTLA-4 mAb and VEGFR-1 (IMC-18F1); anti-BR3 mAb; anti-C. difficile Toxin A and Toxin B C mAbs MDX-066 (CDA-1) and MDX-1388); anti-CD22 dsFv-PE38 conjugates (CAT-3888 and CAT-8015); anti-CD25 mAb (HuMax-TAC); anti-CD3 mAb (NI-0401); adecatumumab; anti-CD30 mAb (MDX-060); MDX-1333 (anti-IFNAR); anti-CD38 mAb (HuMax CD38); anti-CD40L mAb; anti-Cripto mAb; anti-CTGF Idiopathic Pulmonary Fibrosis Phase I Fibrogen (FG-3019); anti-CTLA4 mAb; anti-eotaxin1 mAb (CAT-213); anti-FGF8 mAb; anti-ganglioside GD2 mAb; anti-ganglioside GM2 mAb; anti-GDF-8 human mAb (MYO-029); anti-GM-CSF Receptor mAb (CAM-3001); anti-HepC mAb (HuMax HepC); anti-IFNα mAb (MEDI-545, MDX-198); anti-IGF1R mAb; anti-IGF-1R mAb (HuMax-Inflam); anti-IL12 mAb (ABT-874); anti-IL12/IL23 mAb (CNTO 1275); anti-IL13 mAb (CAT-354); anti-IL2Ra mAb (HuMax-TAC); anti-IL5 Receptor mAb; anti-integrin receptors mAb (MDX-018, CNTO 95); anti-IP10 Ulcerative Colitis mAb (MDX-1100); BMS-66513; anti-Mannose Receptor/hCGβ mAb (MDX-1307); anti-mesothelin dsFv-PE38 conjugate (CAT-5001); anti-PD1mAb (MDX-1106 (ONO-4538)); anti-PDGFRα antibody (IMC-3G3); anti-TGFß mAb (GC-1008); anti-TRAIL Receptor-2 human mAb (HGS-ETR2); anti-TWEAK mAb; anti-VEGFR/Flt-1 mAb; and anti-ZP3 mAb (HuMax-ZP3).

[0071] In some embodiments, the drug delivery device may contain or be used with a sclerostin antibody, such as but not limited to romosozumab, blosozumab, BPS 804 (Novartis), Evenity™ (romosozumab-aqqg), another product containing romosozumab for treatment of postmenopausal osteoporosis and/or fracture healing and in other embodiments, a monoclonal antibody (IgG) that binds human Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9). Such PCSK9 specific antibodies include, but are not limited to, Repatha® (evolocumab) and Praluent® (alirocumab). In other embodiments, the drug delivery device may contain or be used with rilotumumab, bixalomer, trebananib, ganitumab, conatumumab, motesanib diphosphate, brodalumab, vidupiprant or panitumumab. In some embodiments, the reservoir of the drug delivery device may be filled with, or the device can be used with IMLYGIC® (talimogene laherparepvec) or another oncolytic HSV for the treatment of melanoma or other cancers including but are not limited to OncoVEXGALV/CD; OrienX010; G207, 1716; NV1020; NV12023; NV1034; and NV1042. In some embodiments, the drug delivery device may contain or be used with endogenous tissue inhibitors of metalloproteinases (TIMPs) such as but not limited to TIMP-3. In some embodiments, the drug delivery device may contain or be used with Aimovig® (erenumab-aooe), anti-human CGRP-R (calcitonin gene-related peptide type 1 receptor) or another product containing erenumab for the treatment of migraine headaches. Antagonistic antibodies for human calcitonin gene-related peptide (CGRP) receptor such as but not limited to erenumab and bispecific antibody molecules that target the CGRP receptor and other headache targets may also be delivered with a drug delivery device of the present disclosure. Additionally, bispecific T cell engager (BiTE®) antibodies such as but not limited to BLINCYTO® (blinatumomab) can be used in or with the drug delivery device of the present disclosure. In some embodiments, the drug delivery device may contain or be used with an APJ large molecule agonist such as but not limited to apelin or analogues thereof. In some embodiments, a therapeutically effective amount of an anti-thymic stromal lymphopoietin (TSLP) or TSLP receptor antibody is used in or with the drug delivery device of the present disclosure. In some embodiments, the drug delivery device may contain or be used with Avsola™ (infliximab-axxq), anti-TNF α monoclonal antibody, biosimilar to Remicade® (infliximab) (Janssen Biotech, Inc.) or another product containing infliximab for the treatment of autoimmune diseases. In some embodiments, the drug delivery device may contain or be used with Kyprolis® (carfilzomib), (2S)-N-((S)-1-((S)-4-methyl-1-((R)-2-methyloxiran-2-yl)-1-oxopentan-2-ylcarbamoyl)-2-phenylethyl)-2-((S)-2-(2-morpholinoacetamido)-4-phenylbutanamido)-4-methylpentanamide, or another product containing carfilzomib for the treatment of multiple myeloma. In some embodiments, the drug delivery device may contain or be used with Otezla® (apremilast), N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo- 1H-isoindol-4-yl]acetamide, or another product containing apremilast for the treatment of various inflammatory diseases. In some embodiments, the drug delivery device may contain or be used with Parsabiv™ (etelcalcetide HCl, KAI-4169) or another product containing etelcalcetide HCl for the treatment of secondary hyperparathyroidism (sHPT) such as in patients with chronic kidney disease (KD) on hemodialysis. In some embodiments, the drug delivery device may contain or be used with ABP 798 (rituximab), a biosimilar candidate to Rituxan®/MabThera™, or another product containing an anti-CD20 monoclonal antibody. In some embodiments, the drug delivery device may contain or be used with a VEGF antagonist such as a non-antibody VEGF antagonist and/or a VEGF-Trap such as aflibercept (Ig domain 2 from VEGFR1 and Ig domain 3 from VEGFR2, fused to Fc domain of IgG1). In some embodiments, the drug delivery device may contain or be used with ABP 959 (eculizumab), a biosimilar candidate to Soliris®, or another product containing a monoclonal antibody that specifically binds to the complement protein C5. In some embodiments, the drug delivery device may contain or be used with Rozibafusp alfa (formerly AMG 570) is a novel bispecific antibody-peptide conjugate that simultaneously blocks ICOSL and BAFF activity. In some embodiments, the drug delivery device may contain or be used with Omecamtiv mecarbil, a small molecule selective cardiac myosin activator, or myotrope, which directly targets the contractile mechanisms of the heart, or another product containing a small molecule selective cardiac myosin activator. In some embodiments, the drug delivery device may contain or be used with Sotorasib (formerly known as AMG 510), a $KRAS^{G12C}$ small molecule inhibitor, or another product containing a $KRAS^{G12C}$ small molecule inhibitor. In some embodiments, the drug delivery device may contain or be used with Tezepelumab, a human monoclonal antibody that inhibits the action of

thymic stromal lymphopoietin (TSLP), or another product containing a human monoclonal antibody that inhibits the action of TSLP. In some embodiments, the drug delivery device may contain or be used with rocatinlimab (AMG 451), a human anti-OX40 monoclonal antibody that is expressed on activated T cells and blocks OX40 to inhibit and/or reduce the number of OX40 pathogenic T cells that are responsible for driving system and local atopic dermatitis inflammatory responses. In some embodiments, the drug delivery device may contain or be used with AMG 714, a human monoclonal antibody that binds to Interleukin-15 (IL-15) or another product containing a human monoclonal antibody that binds to Interleukin-15 (IL-15). In some embodiments, the drug delivery device may contain or be used with AMG 890, a small interfering RNA (siRNA) that lowers lipoprotein(a), also known as Lp(a), or another product containing a small interfering RNA (siRNA) that lowers lipoprotein(a). In some embodiments, the drug delivery device may contain or be used with ABP 654 (human IgG1 kappa antibody), a biosimilar candidate to Stelara®, or another product that contains human IgG1 kappa antibody and/or binds to the p40 subunit of human cytokines interleukin (IL)-12 and IL-23. In some embodiments, the drug delivery device may contain or be used with Amjevita™ or Amgevita™ (formerly ABP 501) (mab anti-TNF human IgG1), a biosimilar candidate to Humira®, or another product that contains human mab anti-TNF human IgG1. In some embodiments, the drug delivery device may contain or be used with AMG 160, or another product that contains a half-life extended (HLE) anti-prostate-specific membrane antigen (PSMA) x anti-CD3 BiTE® (bispecific T cell engager) construct. In some embodiments, the drug delivery device may contain or be used with AMG 119, or another product containing a delta-like ligand 3 (DLL3) CAR T (chimeric antigen receptor T cell) cellular therapy. In some embodiments, the drug delivery device may contain or be used with AMG 119, or another product containing a delta-like ligand 3 (DLL3) CAR T (chimeric antigen receptor T cell) cellular therapy. In some embodiments, the drug delivery device may contain or be used with AMG 133, or another product containing a gastric inhibitory polypeptide receptor (GIPR) antagonist and GLP-1R agonist. In some embodiments, the drug delivery device may contain or be used with AMG 171 or another product containing a Growth Differential Factor 15 (GDF15) analog. In some embodiments, the drug delivery device may contain or be used with AMG 176 or another product containing a small molecule inhibitor of myeloid cell leukemia 1 (MCL-1). In some embodiments, the drug delivery device may contain or be used with AMG 199 or another product containing a half-life extended (HLE) bispecific T cell engager construct (BiTE®). In some embodiments, the drug delivery device may contain or be used with AMG 256 or another product containing an anti-PD-1 x IL21 mutein and/or an IL-21 receptor agonist designed to selectively turn on the Interleukin 21 (IL-21) pathway in programmed cell death-1 (PD-1) positive cells. In some embodiments, the drug delivery device may contain or be used with AMG 330 or another product containing an anti-CD33 x anti-CD3 BiTE® (bispecific T cell engager) construct. In some embodiments, the drug delivery device may contain or be used with AMG 404 or another product containing a human anti-programmed cell death-1(PD-1) monoclonal antibody being investigated as a treatment for patients with solid tumors. In some embodiments, the drug delivery device may contain or be used with AMG 427 or another product containing a half-life extended (HLE) anti-fms-like tyrosine kinase 3 (FLT3) x anti-CD3 BiTE® (bispecific T cell engager) construct. In some embodiments, the drug delivery device may contain or be used with AMG 430 or another product containing an anti-Jagged-1 monoclonal antibody. In some embodiments, the drug delivery device may contain or be used with AMG 506 or another product containing a multi-specific FAP x 4-1BB-targeting DARPin® biologic under investigation as a treatment for solid tumors. In some embodiments, the drug delivery device may contain or be used with AMG 509 or another product containing a bivalent T-cell engager and is designed using XmAb® 2+1 technology. In some embodiments, the drug delivery device may contain or be used with AMG 562 or another product containing a half-life extended (HLE) CD19 x CD3 BiTE® (bispecific T cell engager) construct. In some embodiments, the drug delivery device may contain or be used with Efavaleukin alfa (formerly AMG 592) or another product containing an IL-2 mutein Fc fusion protein. In some embodiments, the drug delivery device may contain or be used with AMG 596 or another product containing a CD3 x epidermal growth factor receptor vIII (EGFRvIII) BiTE® (bispecific T cell engager) molecule. In some embodiments, the drug delivery device may contain or be used with AMG 673 or another product containing a half-life extended (HLE) anti-CD33 x anti-CD3 BiTE® (bispecific T cell engager) construct. In some embodiments,

the drug delivery device may contain or be used with AMG 701 or another product containing a half-life extended (HLE) anti-B-cell maturation antigen (BCMA) x anti-CD3 BiTE® (bispecific T cell engager) construct. In some embodiments, the drug delivery device may contain or be used with AMG 757 or another product containing a half-life extended (HLE) anti- delta-like ligand 3 (DLL3) x anti-CD3 BiTE® (bispecific T cell engager) construct. In some embodiments, the drug delivery device may contain or be used with AMG 910 or another product containing a half-life extended (HLE) epithelial cell tight junction protein claudin 18.2 x CD3 BiTE® (bispecific T cell engager) construct.

[0072] Although the drug delivery devices, assemblies, components, subsystems and methods have been described in terms of exemplary embodiments, they are not limited thereto. The detailed description is to be construed as exemplary only and does not describe every possible embodiment of the present disclosure. Numerous alternative embodiments could be implemented, using either current technology or technology developed after the filing date of this patent that would still fall within the scope of the claims defining the invention(s) disclosed herein.

[0073] Those skilled in the art will recognize that a wide variety of modifications, alterations, and combinations can be made with respect to the above-described embodiments without departing from the spirit and scope of the invention(s) disclosed herein, and that such modifications, alterations, and combinations are to be viewed as being within the ambit of the inventive concept(s).

What is claimed is:

1. A method of assessing stopper movement in a syringe, the syringe comprising a syringe barrel and a stopper movably disposed within the syringe barrel, the method comprising:

inoculating a biological particulate through an open proximal end of the syringe barrel such that the biological particulate covers at least a portion of an interface between a proximal face of the stopper and an inner wall of the syringe barrel, wherein a cavity of the syringe contains a fill volume of liquid;

subjecting the syringe to one or more conditions;

extracting the fill volume of liquid from the cavity of the syringe;

performing a sterility test on the extracted fill volume of liquid; and

determining stopper movement in the syringe based on the sterility test.

2. The method of claim 1, wherein subjecting the syringe to one or more conditions comprises at least one of: externally sterilizing the syringe, subjecting the syringe to shipping and handling conditions, or performing a manufacturing process with the syringe.

3. The method of claim 1, wherein subjecting the syringe to one or more conditions comprises externally sterilizing the syringe, wherein externally sterilizing the syringe comprises:

placing the syringe in a sterilization chamber;

introducing a dose of sterilant gas into the sterilization chamber and applying a predetermined vacuum level;

holding the vacuum level for a predetermined dwell time; and

purging the sterilization chamber of at least substantially all of the sterilant gas.

4. The method of claim 1, wherein the stopper comprises a body portion having a generally cylindrical sidewall and one or more ribs projecting radially outwardly from the sidewall of the body portion near the proximal face of the stopper, wherein the one or more ribs of the stopper are configured to form a fluid-tight relationship with the cavity of the syringe.

5. The method of claim 4, further comprising inoculating the biological particulate through the open proximal end of the syringe barrel such that the biological particulate covers at least a portion of an interface between the one or more ribs near the proximal face of the stopper and the inner wall of the syringe barrel.

6. The method of claim 1, wherein the biological particulate is inoculated at a plurality of locations around a diameter of the proximal face of the stopper along the interface between the proximal face of the stopper and the inner wall of the syringe barrel.

7. The method of claim 1, wherein the biological particulate comprises at least one of: a microorganism, a fungus, a bacterium, a spore, a virus, a biological cell, a biological antigen, a protein, or a protein antigen.

8. The method of claim 1, wherein performing a sterility test on the extracted liquid comprises:

suspending the extracted liquid into a testing medium containing Trypticase Soy Broth (TSB) or Fluid Thioglycollate Medium (FTM); and

determining whether the extracted liquid contains the biological particulate,

wherein a presence of the biological particulate in the extracted liquid is indicative of stopper movement in the syringe.

9. The method of claim 1, wherein the fill volume of liquid comprises a testing medium containing Trypticase Soy Broth (TSB) or Fluid Thioglycollate Medium (FTM), and wherein performing a sterility test on the extracted liquid comprises determining whether the extracted liquid contains the biological particulate.

10. The method of claim 1, wherein the syringe barrel comprises a distal end configured to support a needle.

11. The method of claim 10, wherein the open proximal end of the syringe barrel is configured to receive a plunger rod, the plunger rod being configured to push the stopper in a distal direction towards the distal end of the syringe barrel.

12. The method of claim 1, wherein the syringe is a pre-filled syringe, and wherein the syringe barrel of the pre-filled syringe is configured to contain a medicament.

13. The method of claim 1, wherein the proximal face of the stopper includes a convex surface.

14. The method of claim 1, wherein the proximal face of the stopper includes a plurality of protrusions protruding axially from the proximal face.

15. The method of claim 1, further comprising identifying a risk of drug product contamination based at least on the determined stopper movement, wherein the risk of drug product contamination exists when a distance moved by the stopper is greater than or equal to an axial length of the stopper.

16. A method of determining a risk of drug product contamination in a syringe, the syringe comprising a syringe barrel and a stopper movably disposed within the syringe barrel, the method comprising:

inoculating a biological particulate through an open proximal end of the syringe barrel such that the biological particulate covers at least a portion of an interface between a proximal face of the stopper and an inner wall of the syringe barrel, wherein a cavity of the syringe contains a fill volume of liquid, and wherein the biological particulate comprises at least one of: a microorganism, a fungus, a bacterium, a spore, a virus, a biological cell, a biological antigen, a protein, or a protein antigen;

subjecting the syringe to one or more conditions;

extracting the fill volume of liquid from the cavity of the syringe;

performing a sterility test on the extracted fill volume of liquid;

determining stopper movement in the syringe based on the sterility test; and

identifying a risk of drug product contamination based at least on the determined stopper movement, wherein the risk of drug product contamination exists when a distance moved by the stopper is greater than or equal to an axial length of the stopper.

17. The method of claim 16, wherein subjecting the syringe to one or more conditions comprises at least one of: externally sterilizing the syringe, subjecting the syringe to shipping and handling conditions, or performing a manufacturing process with the syringe.

18. The method of claim 16, wherein subjecting the syringe to one or more conditions comprises externally sterilizing the syringe, wherein externally sterilizing the syringe comprises:

placing the syringe in a sterilization chamber;

introducing a dose of sterilant gas into the sterilization chamber and applying a predetermined vacuum level;

holding the vacuum level for a predetermined dwell time; and

purging the sterilization chamber of at least substantially all of the sterilant gas.

19. The method of claim 16, wherein the stopper comprises a body portion having a generally cylindrical sidewall and one or more ribs projecting radially outwardly from the sidewall of the body portion near the proximal face of the stopper, wherein the one or more ribs of the stopper are configured to form a fluid-tight relationship with the cavity of the syringe.

20. The method of claim 19, further comprising inoculating the biological particulate through the open proximal end of the syringe barrel such that the biological particulate covers at least a portion of an interface between the one or more ribs near the proximal face of the stopper and the inner wall of the syringe barrel.

21. The method of claim 16, wherein the biological particulate is inoculated at a plurality of locations around a diameter of the proximal face of the stopper along the interface between the proximal face of the stopper and the inner wall of the syringe barrel.

22. The method of claim 16, wherein performing a sterility test on the extracted liquid comprises:

suspending the extracted liquid into a testing medium containing Trypticase Soy Broth (TSB) or Fluid Thioglycollate Medium (FTM); and

determining whether the extracted liquid contains the biological particulate,

wherein a presence of the biological particulate in the extracted liquid is indicative of stopper movement in the syringe.

23. The method of claim 16, wherein the fill volume of liquid comprises a testing medium containing Trypticase Soy Broth (TSB) or Fluid Thioglycollate Medium (FTM), and wherein performing a sterility test on the extracted liquid comprises determining whether the extracted liquid contains the biological particulate.

24. The method of claim 16, wherein the syringe barrel comprises a distal end configured to support a needle.

25. The method of claim 24, wherein the open proximal end of the syringe barrel is configured to receive a plunger rod, the plunger rod being configured to push the stopper in a distal direction towards the distal end of the syringe barrel.

26. The method of claim 16, wherein the syringe is a pre-filled syringe, and wherein the syringe barrel of the pre-filled syringe is configured to contain a medicament.

27. The method of claim 16, wherein the proximal face of the stopper includes a convex surface.

28. The method of claim 16, wherein the proximal face of the stopper includes a plurality of protrusions protruding axially from the proximal face.