(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 May 2020 (22.05.2020)

WIPO | PCT

(10) International Publication Number
WO 2020/102434 A2

(51) International Patent Classification:
B29C 49/48 (2006.01)

(21) International Application Number:
PCT/US2019/061293

(22) International Filing Date:
13 November 2019 (13.11.2019)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/760,542 13 November 2018 (13.11.2018) US

(71) Applicant: **SIO2 MEDICAL PRODUCTS, INC.** [US/US]; 2250 Riley Street, Auburn, Alabama 36832 (US).

(72) Inventors: **SADZEWICZ, Eugene**; c/o SiO2 Medical Products, Inc., 2250 Riley Street, Auburn, Alabama 36832 (US). **KELLY, Kenneth Wade**; c/o Sio2 Medical Products, Inc., 2250 Riley Street, Auburn, Alabama 36832 (US). **BALTAZAR, Martin**; c/o Sio2 Medical Products, Inc., 2250 Riley Street, Auburn, Alabama 36832 (US). **BREELAND, Adam**; c/o Sio2 Medical Products, Inc., 2250 Riley Street, Auburn, Alabama 36832 (US). **FISK, Thomas E.**; 1336 N. Sun Catcher Way, Green Valley, Arizona 85614 (US). **HENTON, David**; 5409 Woodview, Midland, Michigan 48642 (US). **MAURER, Brian**; 129 Robertson Road, North Wales, Pennsylvania 19454 (US). **TAHA, Ahmad**; c/o SiO2 Medical Products, Inc., 2250 Riley Street, Auburn, Alabama 36832 (US). **WEIKART, Christopher**; c/o SiO2 Medical Products, Inc., 2250 Riley Street, Auburn, Alabama 36832 (US).

(74) Agent: **GORNISH, David B.**; Sio2 Medical Products, INC., 2570 Boulevard of the Generals, Suite 215, Norristown, Pennsylvania 19403 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO,

(54) Title: POLYMER VIALS WITH SUBSTANTIALLY FLAT BOTTOMS AND INJECTION STRETCH BLOW MOLDING METHODS FOR MAKING THE SAME

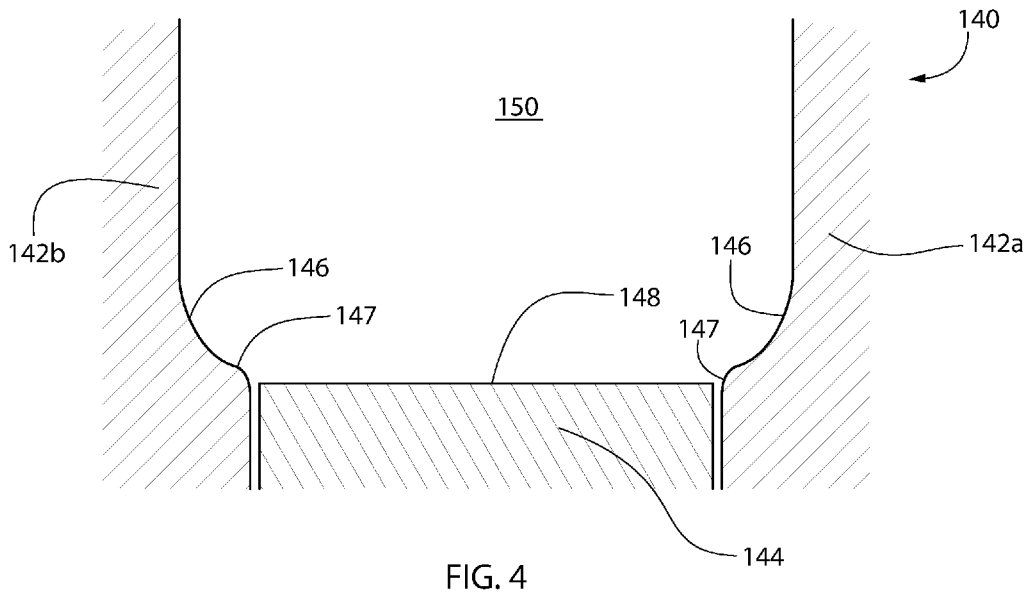


FIG. 4

(57) Abstract: Disclosed are polymer vials and injection stretch blow molding methods for making the same. A polymer vial has a base having a base surface area and a sidewall extending up from the base. The base and sidewall define an interior configured to house product, the sidewall narrowing at an upper section of the vial to form a neck leading to an opening that provides access to the interior. The vial is optionally round and symmetrical about a central axis, a lower portion of the sidewall including a first surface that is outwardly curved along a first radius having an imaginary center positioned within the vial. The base is positioned below the first surface and is substantially flat such that at least 80% of the base surface area has a standing base surface occupying a single plane.

WO 2020/102434 A2

[Continued on next page]

DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

POLYMER VIALS WITH SUBSTANTIALLY FLAT BOTTOMS AND INJECTION STRETCH BLOW MOLDING METHODS FOR MAKING THE SAME

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims priority to U.S. Provisional Patent Application No. 62/760,542, filed November 13, 2018, which is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

1. FIELD OF INVENTION

[0002] The disclosed concept relates to plastic containers or vessels and methods of making the same. More particularly, the disclosed concept relates to injection stretch blow molding techniques for producing vials having substantially flat bottoms. The inventors have found these techniques to better control part side-wall thickness variation and generate vials particularly suitable for parenteral drug storage and lyophilization. The disclosed concept provides vials well suited for preparation, storage and lyophilization of drug products.

2. DESCRIPTION OF RELATED ART

[0003] An important consideration for pharmaceutical packages or vessels, e.g., parenteral vials, is that the contents have a substantial shelf life.

[0004] For decades, most parenteral therapeutics have been delivered to end users in Type I medical grade borosilicate glass vessels such as vials. The relatively strong, impermeable and inert surface of borosilicate glass has performed adequately for most drug products. However, the recent advent of costly, complex and sensitive biologics has exposed the physical and chemical shortcomings of glass pharmaceutical packages, including possible contamination from metals, flaking, delamination, and breakage, among other problems. Moreover, glass contains several components which can leach out during storage and cause damage to the stored material.

[0005] In more detail, borosilicate pharmaceutical packages or other vessels, e.g., vials, exhibit a number of drawbacks. Glass is manufactured from sand containing a heterogeneous mixture of many elements (silicon, oxygen, boron, aluminum, sodium, calcium) with trace levels of other alkali and earth metals. Type I borosilicate glass consists of approximately 76% SiO_2, 10.5% B_2O_3, 5% Al_2O_3, 7% Na_2O and 1.5% CaO and often contains trace metals such as iron, magnesium, zinc, copper and others. The heterogeneous nature of borosilicate glass creates a non-uniform surface chemistry at the

molecular level.

[0006] Glass forming processes used to create glass vessels expose some portions of the vessels to temperatures as great as 1,200° C. Under such high temperatures, alkali ions migrate to the local surface and form oxides. The presence of ions extracted from borosilicate glass devices may be involved in degradation, aggregation and denaturation of some biologics. Many proteins and other biologics must be lyophilized (freeze dried), because they are not sufficiently stable in solution in glass vials.

[0007] Presently, a great number of glass containers are manufactured for use in the lyophilization process, wherein a liquid is placed in a vial type container, partially stoppered to permit escape of the water vapor during the sublimation step, followed by complete stoppering through the application of force onto the stopper along the axis of the container. Glass containers have historically been used for pharmaceutical lyophilization because glass provides the desired clarity, resistance to chemical attack and physical stability for storage of lyophilized drugs. Nonetheless, at least for reasons set forth above, glass presents certain drawbacks for this application. A non-glass solution would be desirable, however, prior to the inventors' development of the disclosed concept, there has been no viable non-glass solution for lyophilization vials.

[0008] Prior to the present application, a theoretical possible non-glass solution could be plastic. However, there are significant challenges associated with making a viable lyophilization vial out of plastic. One such challenge relates to the properties of the material itself. Although plastic is superior to glass with respect to breakage, dimensional tolerances and surface uniformity, its use in primary pharmaceutical packaging remains limited due to certain shortcomings, including gas permeability and leachables/extractables. Regarding gas permeability, plastic allows small molecule gases to permeate through it. This includes, among other things, permeability to oxygen and water vapor. This can be detrimental the shelf life of a lyophilized drug. Regarding leachables and extractables, plastic vessels contain organic compounds that can extract out into the stored drug product. These compounds can contaminate the drug and/or negatively impact the drug's stability.

[0009] The assignee of the present application has developed certain coating technologies and processes that may provide certain benefits of glass on an otherwise plastic vessel. Such coating technologies allow one to leverage the beneficial aspects of plastic, noted above, without the aforementioned countervailing disadvantages. These coating technologies are described below in the

specification in conjunction with their potential use with optional aspects of the disclosed concept. Use of such coatings would solve part of the problem. However, there would still remain challenges associated with utilizing existing blow molding methods/apparatus and standard plastic vial configurations for lyophilization applications. To help explain these challenges, some background regarding the blow molding process and configuration of conventional plastic vials is presented now.

[0010] A "vial," as that term is used herein, refers generally to a rigid or semi-rigid container or vessel having a comparatively narrow neck and/or mouth. A vial is typically symmetrical about its central axis, is optionally round and is preferably clear in appearance so that its contents are clearly visible.

[0011] Bottles or vials may typically be formed using blow molding. Blow molding is a manufacturing process by which hollow plastic parts, e.g., bottles or vials (having a comparatively narrow neck and/or opening), are formed. In general, there are three types of blow molding: (1) extrusion blow molding; (2) injection blow molding; and (3) injection stretch blow molding. In any type of blow molding, the process begins with providing molten plastic and forming it into a parison or preform. The parison is a tube-like piece of plastic with an opening in one end through which compressed air can pass. The parison is clamped into a mold and air is blown into it. The air pressure pushes the plastic out (almost like blowing a balloon) to match the contours of the mold, thus forming a finished part once it has cooled. After the vessel has cooled and hardened, the mold is opened and the part ejected.

[0012] Extrusion blow molding is a process that is substantially as described before but also requires spin trimming, which is an additional step involving cutting excess material away. Extrusion blow molded parts are known to have low strength and are consequently not desirable for most containers. Also, the additional processing steps involved render extrusion blow molding unfavorable for making lyophilization vials.

[0013] In the standard injection blow molding (IBM) process, the polymer is injection molded onto a core pin; then the core pin is rotated to a blow molding station to be inflated and cooled. This is the least-used of the three blow molding processes, and is typically used to make small medical and single serve bottles. The process is divided into three steps: injection, blowing and ejection. The injection blow molding machine is based on an extruder barrel and screw assembly which melts the polymer. The molten polymer is fed into a hot runner manifold where it is injected through nozzles

into a heated cavity and core pin. The cavity mold forms the external shape of the vessel and is clamped around a core rod which forms the internal shape of the preform. The preform consists of a fully formed bottle/jar neck with a thick tube of polymer attached, which will form the body, similar in appearance to a test tube with a threaded neck. An example of such a preform may be found in U.S. Pat. Pub. No. 2009/0220809. The preform mold opens and the core rod is rotated and clamped into the hollow, chilled blow mold. The end of the core rod opens and allows compressed air into the preform, which inflates it to the finished article shape. After a cooling period the blow mold opens and the core rod is rotated to the ejection position. Typically, injection blow molding only suits small capacity bottles as it is difficult to control the base center during blowing. Additionally, there is no increase in barrier strength as the material is not biaxially stretched. Accordingly, standard injection blow molding methods are undesirable for most containers and vessels due to limited uses or product configurations, barrier strength limitations, and other manufacturing disadvantages.

[0014] Traditional injection stretch blow molding (ISBM) is typically carried out using one of two different methods, namely single-stage and two-stage.

[0015] In the two-stage injection stretch blow molding process, the plastic is first molded into a preform using the injection molding process. These preforms are produced with the necks of the bottles, optionally including threads on one end. These preforms are packaged, and fed later (after cooling) into a reheat stretch blow molding machine. In the ISBM process, the preforms are heated above their glass transition temperature, then blown using high-pressure air into bottles using metal blow molds. The preform is always stretched with a core rod or mandrel as part of the process.

[0016] For purposes of providing background to put the disclosed concept in proper context, prior art methods and containers are now described with reference to certain drawing figures. In particular, Fig. 1 illustrates a typical prior art vial 10 that may be made using a blow molding process. The vial 10 includes a base 12 and a sidewall 14 extending up from the base 12. The base 12 and sidewall 14 define an interior 16 configured to house product therein, e.g., a drug product. The sidewall 14 narrows at an upper section of the vial 10 to form a neck 18 leading to an opening 20, from which stored product may be accessed or dispensed. The vial 10 is optionally round and symmetrical about a central axis. As best seen in Fig. 1A, which is an enlarged view of a bottom section of the vial 10 of Fig. 1, the base 12 is convex, forming a dome 26 which extends upwards from a peripheral edge 22 of the base 12. The peripheral edge 22 comprises a standing ring 24,

which forms the lowest portion of the base 12 and is configured to contact a flat support surface onto which the vial may rest when it is oriented upright. In other words, the standing ring 24 serves as a standing base in prior art vial 10.

[0017] Vial 10 of Fig. 1 may be made with a blow molding process using a prior art mold 40, a portion of which is depicted in the schematic drawing of Fig. 2. The mold 40 includes a first mold part 42a and a second mold part 42b, the first and second mold parts 42a,b coming together about a central axis to form the outer shape of the sidewall 14 and standing ring 24 of the vial 10. First and second mold parts 42a,b mirror each other in size and configuration. The mold also includes a "cup style" (i.e., curved and not flat) base mold 44 that is configured to form the outer shape of much of the base 12 of the vial 10. The first mold part 42a, second mold part 42b and base mold 44 together define a mold cavity 50 into which a molten polymer preform or parison may be blown to conform to the surfaces of those parts of the mold 40, thus forming the vial 10.

[0018] The cup style base mold 44 includes a domed surface 48 configured to form the dome 26 of the base 12 of vial 10. The first and second mold parts 42a,b each comprise a ring portion 46 adjacent the base mold 44. The ring portion 46 is positioned slightly lower than the domed surface 48 of the base mold 44. In other words, the base mold 44 protrudes higher than the lowest portions of first and second mold parts 42a,b. The ring portion 46 corresponds to the outer surface of the standing ring 24 of vial 10. The prior art mold 40 thus forms the peripheral edge 22 and standing ring 24 (i.e., the standing surface of vial 10) using first and second mold parts 42a,b – not with the base mold 44.

[0019] Applicant has found that vial 10, mold 40 and the method used to produce vial 10, is not preferred for use in lyophilization. Dimensions and dimensional tolerances of a vial are critical to the thermal efficiency of the vial if used for lyophilization. Existing methods/molds for blow-molding containers or vessels, as described above, are deficient in producing the necessary dimensions and dimensional tolerances for improved thermal efficiency necessary for lyophilization. There is a need for a non-glass lyophilization vial having gas and solute barrier properties which approach the properties of glass. There is a further need for a non-glass vial having a configuration, dimensions and dimensional tolerances that provide optimal thermal efficiency for lyophilization. There is also a need for novel manufacturing equipment and processes which produce thermally efficient containers or vessels (e.g., vials) for lyophilization. Neither prior art vial 10 nor other

plastic containers proposed for parenteral purposes, e.g., those disclosed in U.S. Pat. Nos. 4,415,085, 4,479,989, 4,484,916, 4,592,092, 4,516,977, 4,561,110 and 5,344,036, appear to be useful as a substitute for the glass vials in conventional lyophilization processes.

SUMMARY OF THE INVENTION

[0020] Accordingly, in one optional embodiment, a polymer vial is provided. The vial includes a base having a base surface area, a sidewall extending up from the base, the base and sidewall defining an interior configured to house product. The sidewall narrows at an upper section of the vial to form a neck leading to an opening that provides access to the interior. The vial is optionally round and symmetrical about a central axis, a lower portion of the sidewall including a first surface that is outwardly curved along a first radius having an imaginary center positioned within the vial. The base is positioned below the first surface and is substantially flat such that at least 80% of the base surface area, optionally at least 85% of the base surface area, optionally at least 90% of the base surface area, includes a standing base surface occupying a single plane.

[0021] Optionally, in any embodiment of a vial according to the disclosed concept, the vial is made from a clear thermoplastic material, optionally a polyolefin.

[0022] Optionally, in any embodiment of a vial according to the disclosed concept, the base in its entirety is positioned below the first surface.

[0023] Optionally, in any embodiment of a vial according to the disclosed concept, the vial further includes a second surface that extends from and is positioned below the first surface. The second surface is inwardly curved along a second radius having an imaginary center positioned outside of the vial. The second surface terminates at a peripheral edge of the base from which the standing base surface extends inwardly towards the central axis. The standing base is configured to contact and rest on a flat support surface so as to orient the vial in an upright position.

[0024] Optionally, in any embodiment of a vial according to the disclosed concept, the vial is produced by an injection stretch blow molding process.

[0025] Optionally, in any embodiment of a vial according to the disclosed concept, the vial is made from an olefin polymer or copolymer, optionally cyclic olefin polymer or cyclic olefin copolymer.

[0026] Optionally, in any embodiment of a vial according to the disclosed concept, the vial wall includes a PECVD water barrier coating or layer having a water contact angle of from 80 to 180

degrees, optionally from larger than 80 degrees to less than 180 degrees, optionally from 90 degrees to 160 degrees, optionally from 100 degrees to 150 degrees, optionally from 110 degrees to 150 degrees. Optionally, the PECVD water barrier coating or layer is applied through a process that includes: in a PECVD apparatus, supplying a water barrier coating or layer precursor to the vial and creating a plasma using the same, the water barrier coating or layer precursor comprising as least one of a saturated or unsaturated, linear or cyclic aliphatic fluorocarbon precursor having from 1 to 10, optionally 1 to 6, optionally 2 to 6 carbon atoms and from 4 to 20 fluorine atoms per molecule, optionally hexafluropropylene (C_3F_6), octafluorocyclobutane (C_4F_8), tetrafluoroethylene (C_2F_4), hexafluoroethane (C_2F_6), hexafluoropropylene (C_3F_6), octafluorocyclobutane (C_4F_8), perfluorohexane (C_6F_{14}) or perfluoro-2-methyl-2-pentene (C_6F_{12}), the water barrier coating or layer precursor further comprising a saturated or unsaturated hydrocarbon having from 1 to 6 carbon atoms, for example lower alkanes having from 1 to 4 carbon atoms, alkenes or alkynes having from 2 to 4 carbon atoms, for example acetylene (C_2H_2) or methane (CH_4), optionally acetylene (C_2H_2), a saturated or unsaturated hydrofluorocarbon having from 1 to 6 carbon atoms, or any combination thereof. Optionally, in any embodiment of the vial, a PECVD tri-layer coating set (having a tri-layer, SiOx barrier layer and pH protective layer) is deposited onto the PECVD water barrier layer.

[0027] Optionally, in any embodiment of a vial according to the disclosed concept, the polymer vial of any previous claim further comprising a cap to fully or partially close the opening.

[0028] Optionally, in any embodiment of a vial according to the disclosed concept, the vial has drug contents stored in the interior space, wherein the drug contents optionally comprise biologic drugs, gene therapy or viral vectors.

[0029] In an optional aspect of the disclosed concept, a method for making a polymer vial by injection stretch blow molding is provided. The method includes providing a mold, the mold having a first mold part and a second mold part. The first mold part and second mold part are configured to meet along a central axis to form an outer shape of a sidewall of the vial. Respective interior sizes and configurations of the first mold part and second mold part mirror each other. The mold further includes a base mold configured to form a base of the vial. The base mold has a substantially flat molding surface, wherein at least 80%, optionally at least 85%, optionally at least 90%, of the molding surface of the base mold occupies a single plane. The first mold part, second mold part and base mold together define a mold cavity when the mold is in a blowing position in which the base

mold is in position relative to the first and second mold parts to form the base of the vial. The method further includes providing a mandrel within the mold and a molten polymer preform onto the mandrel, stretching the preform with the mandrel to extend an end thereof optionally past respective molding surfaces of the first mold part and second mold part, optionally wherein the base mold is axially distal to the base mold location when the mold is in the blowing position. The method further includes moving the base mold axially towards the first mold part and second mold part to place the mold in the blowing position. The method further includes blowing gas into the preform such that the preform expands within the molding space and conforms to respective surfaces of the first mold part, second mold part and the base mold, when the mold is in the blowing position, wherein the substantially flat molding surface of the base mold is positioned entirely axially below respective molding surfaces of the first mold part and second mold part.

[0030] Optionally, in any embodiment of the method for making a polymer vial by injection stretch blow molding according to the disclosed concept, neither the first mold part nor the second mold part form any portion of the base of the vial.

[0031] Optionally, in any embodiment of the method for making a polymer vial by injection stretch blow molding according to the disclosed concept, the base mold forms no portion of the sidewall of the vial.

[0032] Optionally, in any embodiment of the method for making a polymer vial by injection stretch blow molding according to the disclosed concept, each of the first mold part and second mold part include a first curved mold surface that leads to a second curved mold surface. The first curved mold surface follows a radius with an imaginary center positioned in the mold cavity. The second curved mold surface follows a radius with an imaginary center positioned outside the mold cavity. These curves and radii are from the perspective of a cross sectional view, it being understood that the geometry of the mold and corresponding vial is three dimensional around the perimeter or circumference of the mold and corresponding vial. Optionally, no portion of the substantially flat molding surface of the base mold extends axially above the second curved mold surface.

[0033] Optionally, the disclosed concept relates to a polymer vial, optionally clear thermoplastic vial made by any of the methods disclosed herein.

[0034] In an optional aspect, the disclosed concept relates to a method including providing a polymer vial according to any embodiment disclosed herein that is filled with a product in solution

form and lyophilizing the product to render a dry powdered lyophilized form of the product within the vial.

[0035] In an optional aspect of the disclosed concept, a mold for making a vial is provided. The mold includes a first mold part and a second mold part, the first mold part and second mold part being configured to meet along a central axis (i.e., central axial plane) to form an outer shape of a sidewall of the vial. Respective interior sizes and configurations of the first mold part and second mold part mirror each other. The mold further includes a base mold configured to form a base of the vial, the base mold having a substantially flat molding surface, wherein at least 80%, optionally at least 85%, optionally at least 90%, optionally all, of the molding surface of the base mold occupies a single plane. The first mold part, second mold part and base mold together define a mold cavity when the mold is in a blowing position in which the base mold is in position relative to the first and second mold parts to form the base of the vial, such that the substantially flat molding surface of the base mold is positioned entirely axially below respective molding surfaces of the first mold part and second mold part. Optionally, neither the first mold part nor the second mold part are configured to form any portion of the base of the vial. Optionally, the base mold is configured to form no portion of the sidewall of the vial. Optionally, each of the first mold part and second mold part include a first curved mold surface that leads to a second curved mold surface, the first curved mold surface following a radius with an imaginary center positioned in the mold cavity, the second curved mold surface following a radius with an imaginary center positioned outside the mold cavity. Optionally, no portion of the substantially flat molding surface of the base mold extends axially above the second curved mold surface.

[0036] Optionally, in any embodiment of a vial according to the disclosed concept, a lyophilized product is stored within the interior, the lyophilized product configured to be reconstituted into a liquid product. Optionally, the lyophilized product is a biologic drug, a gene therapy or viral vector.

[0037] Optionally, in any embodiment, the vial of the disclosed concept may more generally be referred to as container or vessel.

BRIEF DESCRIPTION OF SEVERAL VIEWS OF THE DRAWINGS

[0038] The background of the invention and the invention itself will be described in conjunction with the following drawings in which like reference numerals designate like elements and wherein:

[0039] Fig. 1 is a simplified section view of a prior art vial formed by a blow molding process.

[0040] Fig. 1A is an enlarged view of a bottom section of the vial of Fig. 1.

[0041] Fig. 2 is a simplified schematic drawing of a portion of a prior art blow mold that may be used to form the vial of Fig. 1.

[0042] Fig. 3 is a simplified section view of a vial formed by a blow molding process, optionally injection stretch blow molding process, in accordance with an optional aspect of the disclosed concept.

[0043] Fig. 3A is an enlarged view of a portion of the vial of Fig. 3.

[0044] Fig. 4 is a simplified schematic drawing of a portion of a blow mold according to an optional aspect of the disclosed concept that may be used to form the vial of Fig. 3.

[0045] Figs. 5A-5C show a schematic illustration of the steps involved in injection stretch blow molding a vial in accordance with an optional aspect of the disclosed concept.

[0046] Fig. 6A is a schematic illustration of a bottom-right section of an exemplary 10 mL lyophilization vial according to an optional aspect of the disclosed concept, which shows exemplary dimensions dimensional tolerances of the vial, in mm.

[0047] Fig. 6B is a schematic illustration of a bottom-right section of an exemplary 20 mL lyophilization vial according to an optional aspect of the disclosed concept, which shows exemplary dimensions and dimensional tolerances of the vial, in mm.

[0048] Fig. 7 shows a schematic diagram of a PECVD apparatus that may be used to apply PECVD layers, e.g., surface barrier coatings or layers and/or protective or passivation coatings or layers, in accordance with at least one optional aspect of the disclosed concept.

[0049] Fig. 8 is a graph comparing dimensional variability of polymer vials according to the disclosed concept and prior art glass vials.

[0050] Fig. 9 is a graph showing parameters of the lyophilization cycle used for an exemplary study comparing glass vials with COP vials in accordance with optional embodiments of the disclosed concept.

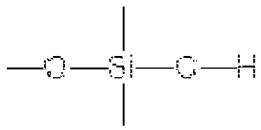
DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS OF THE INVENTION

[0051] The disclosed concept will now be described more fully with reference to the accompanying drawings, in which several embodiments are shown. This invention may, however, be embodied in many different forms and should not be construed as limited to the embodiments set forth here. Rather, these embodiments are examples of the invention, which has the full scope

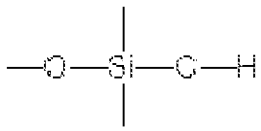
indicated by the language of the claims. Like numbers refer to like elements throughout. Unless indicated otherwise, the features characterizing the embodiments and aspects described in the following may be combined with each other, and the resulting combinations are also embodiments of the present invention.

Definitions

[0052] As used in this disclosure, an "organosilicon precursor" is a compound having at least one of the linkages:



or



which is a tetravalent silicon atom connected to an oxygen or nitrogen atom and an organic carbon atom (an organic carbon atom being a carbon atom bonded to at least one hydrogen atom). A volatile organosilicon precursor, defined as such a precursor that can be supplied as a vapor in a plasma enhanced chemical vapor deposition (PECVD) apparatus, is an optional organosilicon precursor. Optionally, the organosilicon precursor is selected from the group consisting of a linear siloxane, a monocyclic siloxane, a polycyclic siloxane, a polysilsesquioxane, an alkyl trimethoxysilane, a linear silazane, a monocyclic silazane, a polycyclic silazane, a polysilsesquiazane, and a combination of any two or more of these precursors. Preferably, the organosilicon precursor is octamethylcyclotetrasiloxane (OMCTS). Values of w, x, y, and z are applicable to the empirical composition $Si_wO_xC_yH_z$ throughout this specification. The values of w, x, y, and z used throughout this specification should be understood as ratios or an empirical formula (for example for a coating or layer), rather than as a limit on the number or type of atoms in a molecule. For example, octamethylcyclotetrasiloxane, which has the molecular composition $Si_4O_4C_8H_{24}$, can be described by the following empirical formula, arrived at by dividing each of w, x, y, and z in the molecular formula by 4, the largest common factor: $Si_1O_1C_2H_6$. The values of w, x, y, and z are also not limited to integers. For example, (acyclic) octamethyltrisiloxane, molecular composition $Si_3O_2C_8H_{24}$, is reducible to $Si_1O_{0.67}C_{2.67}H_8$. Also, although $SiO_xC_yH_z$ is described as equivalent to

SiO_xC_y, it is not necessary to show the presence of hydrogen in any proportion to show the presence of SiO_xC_y.

[0053] "PECVD" refers to plasma enhanced chemical vapor deposition.

Optional Vial Configuration and Equipment and Process for Molding

[0054] Fig. 3 illustrates an optional embodiment of a vial 110 according to the disclosed concept. The vial 110 may be made using an injection stretch blow molding process, as explained in detail, below. The vial 110 includes a base 112 and a sidewall 114 extending up from the base 112. The base 112 and sidewall 114 define an interior 116 configured to house product therein, e.g., a lyophilized drug product. The sidewall 114 narrows at an upper section of the vial 110 to form a neck 118 leading to an opening 120, from which stored product may be accessed or dispensed. The vial 110 is preferably round and symmetrical about a central axis. As best seen in Fig. 3A, which is an enlarged view of a bottom left section of the vial 110 of Fig. 1, the base 112 is flat. In a preferred embodiment, the base 112 is completely flat, with the possible exception of slight relief in the gate area, as an artifact of the injection stretch blow molding process. With a substantially or completely flat base 112, the vial 110 comprises a flat standing base 124, which is configured to contact a flat support surface (e.g., tabletop or lyophilization shelf) onto which the vial may rest when it is oriented upright. The standing base 124 provides a horizontal rest surface for the vial 110. The flat standing base 124 helps to facilitate heat transfer into the vial 110 and thus provides a vial 110 that is more thermally efficient, e.g., for lyophilization, than prior art vial 10 of Fig. 1.

[0055] As noted above, the base 112 is completely or at least substantially flat. Optionally, in any embodiment, at least 80% of the base 112 surface area comprises a surface occupying a single plane. Optionally, in any embodiment, at least 85% of the base 112 surface area comprises a surface occupying a single plane. Optionally, in any embodiment, at least 90% of the base 112 surface area comprises a surface occupying a single plane. Optionally, in any embodiment, at least 95% of the base 112 surface area comprises a surface occupying a single plane. Optionally, in any embodiment, 100% of the base 112 surface area comprises a surface occupying a single plane. Optionally, in any embodiment, 80% to 100%, optionally 85% to 100%, optionally 90% to 100%, optionally 85% to 99%, optionally 90% to 99%, of the base 112 surface area comprises a surface occupying a single plane.

[0056] The sidewall 114, at a lower portion thereof, optionally includes a first surface 113 comprising an outer radius 115, which leads to a second surface 117 comprising an inner radius 119. The term "outer radius" here refers to a radius that is outwardly curved (relative to the vial), having an imaginary center positioned within the vial. The first surface 113 curve is preferably less than 90°. The term "inner radius" here refers to a radius that is inwardly curved (relative to the vial), having an imaginary center positioned outside of the vial. Optionally, the inner radius 119 is smaller, optionally substantially smaller, than the outer radius 115. For example, the inner radius 119 is optionally at least 100 times smaller, optionally at least 50 times smaller, optionally at least 20 times smaller, optionally at least 10 times smaller, optionally at least 5 times smaller, optionally at least 2 times smaller than the outer radius 115. Optionally, the inner radius 119 is 2-50 times smaller, optionally 2-20 times smaller, optionally 2-10 times smaller, optionally 2-5 times smaller than the outer radius 115. The second surface 117 terminates at a peripheral edge 122 of the base 112. The standing base 124 extends inward from the peripheral edge 122.

[0057] Vial 110 may be made with an injection stretch blow molding process using mold 140, a portion of which is depicted in the schematic drawing of Fig. 4. The mold includes a first mold part 142a and a second mold part 142b, the first and second mold parts 142a,b coming together at a central axis (i.e., central axial plane) to form the outer shape of the sidewall 114 of the vial 110. First and second mold parts 142a,b mirror each other in size and configuration. The mold 140 also includes a "push up style" base mold 144 that is configured to form the outer shape of the entire base 112 of the vial 110. The first mold part 142a, second mold part 142b and base mold 144 together define a mold cavity 150 into which a molten polymer preform may be stretched and then blown to conform to the surfaces of those parts of the mold 140, thus forming the vial 110.

[0058] The push up style base mold 144 includes a flat or planar molding surface 148 configured to form the flat standing base 124 of the base 112 of vial 110. The first and second mold parts 142a,b each comprise a first curved mold surface 146 leading to a second curved mold surface 147. The first curved mold surface 146 has a radius with an imaginary center positioned in the mold cavity 150. The second curved mold surface 147 has a radius with an imaginary center positioned in each respective mold part 142a,b (i.e., outside the mold cavity 150). First curved mold surface 146 forms the outer shape of the first surface 113 of the sidewall 114 of vial 110. Second curved mold surface 147 forms the outer shape of the second surface 117 of the sidewall 114 of the vial 110.

These curves and radii are from the perspective of a cross sectional view, it being understood that the geometry of the mold and corresponding vial is three dimensional around the perimeter or circumference of the mold and corresponding vial.

[0059] Notably, the base mold 144 and its flat or planar molding surface 148 sit below the lowest molding surfaces (e.g., the second curved mold surface 147) of the first and second mold parts 142a,b when the corresponding vial 110 is formed. This stands in contrast with the prior art mold 40 of Fig. 2, in which the base mold 44 projects above the lowest molding surfaces of the first and second mold parts 42a,b. As a consequence, the prior art vial 10 of Fig. 1 has a standing base (in that case, standing ring 24) which is formed by the first and second mold parts 42a,b, while, by contrast, the vial 110 of the disclosed concept (Figs. 3 and 3A) has a standing base 124, which is formed by the base mold 144. Another important difference is that the base 12 of prior art vial 10 is domed while base 112 of the vial 110 of the disclosed concept is completely flat (with the possible exception of slight relief in the gate area). Likewise, the base mold 144 molding surface 148 of mold 140 is completely flat, with the possible optional exception of a very slight center indent to ensure the gate isn't protruding, in contrast to the domed surface 48 of prior art base mold 44.

[0060] The aforementioned structural features of mold 140 and corresponding vial 110, in combination with optional injection stretch blow molding processes, result in a plastic vial 110 that is very thermally efficient and thus ideal for lyophilization. An overview of the injection stretch blow molding process as applied to the disclosed concept is now provided, followed by a description of optional features and advantages of the vial 110.

[0061] Figs. 5A-5C show a schematic illustration of the steps involved in stretch blow molding according to an aspect of the disclosed concept. It is noted that the final vial shown in Fig. 5C is intended to be merely illustrative of the process and does not precisely and intricately depict all structural features of vial 110. As shown in Fig. 5A, injection stretch blow molding initially involves steps of: providing a plastic resin 202 (e.g., cyclin olefin polymer), melting the resin and delivering the melt to an injection mold 204, and molding a preform 206 from the resin. In a next step 208, as shown in Fig. 5B, the heated preform is stretched optionally within the mold using a mandrel. When in the mold, the preform is stretched past the bottom (i.e., the base mold is not yet in position for blowing such that the mold is not in blow position). In a last step 210, as shown in Fig. 5C, gas is blown into the stretched heated preform while the mold parts and base mold are collectively in blow

position (i.e., the base mold is pushed up from its previous position during the stretch step) to form the final shape of the vial. Moving the base mold up in this way after stretching and then blowing gas helps to optimize material distribution, especially in the corners. Blow pressure may be adjusted and controlled during steps 208 and 210. For example, optionally low pressure blow may be utilized during the stretch step 208 to help distribute the material of the preform out. Gas may be blown at high pressure when the base mold is in position, after the desired shape of the vial is partially formed. Optionally, a four component injection mold is used to help optimize the process and result in improved material distribution.

[0062] During the stretching step, the mandrel may be controlled pneumatically or by servo. Servo may be preferred because it provides more precise control in stretch speed and position of the mandrel. Also, a servo may optionally be used to monitor plastic temperature and adjust speed profile to help achieve a vial with desirable dimensions and tolerance necessary for thermal efficiency.

[0063] Applicant has found that the lower stretch ratio produced using injection stretch blow molding compared to other forms of blow molding enables better control of the part side wall thickness variation. Dimensional control and tolerances of the resulting part can improve the thermal efficiency of the container or vessel (e.g., vial). Minimizing side wall thickness variation facilitates more consistent heat transfer during a freeze drying (lyophilization) cycle. Notably, consistent side wall thickness measured radially (i.e., 360° around a central axis of the vial) appears to be more important than consistency of wall thickness measured axially (i.e., wall thickness at the top of the vial versus that near the bottom). In addition to advantages relating to thermal efficiency, sidewall thickness consistency of a vial produced according to the injection stretch blow molding method of the disclosed concept results in improved optical properties. Such properties in parenteral containers is necessary to permit visual inspection through the clear container for any foreign contamination. Side wall thickness inconsistency can create optical distortion, which limits one's ability to visually inspect the contents of the vial. The methods and vials of the disclosed concept reduce or eliminate this problem of the prior art.

[0064] It has further been found that density of the polymer vials made according to the above-noted process is much more consistent and precisely controlled than that of glass vials. Variations in density can affect the cycle time for lyophilization. Thus, the more consistent density of the vials

according to the disclosed concept provide improved consistency in the lyophilization process.

[0065] Referring to Figs. 6A and 6B, there are respectively shown schematic illustrations of bottom-right sections of exemplary 10 mL (Fig. 6A) and 20mL (Fig. 6B) lyophilization vials according to optional aspects of the disclosed concept, which show optional dimensions and dimensional tolerances of the vials. The dimensions and ranges shown in the figures are in millimeters. These dimensional tolerances are based on measurements of actual parts produced with injection stretch blow molding methods and equipment according to optional aspects of the disclosed concept. The dimensional contour thickness varies by less than 0.03 mm from part to part. The thickness does vary across the bottom by 0.5 mm on the 20ml (with preform and process optimized), but the contour is practically the same from part to part. Even with the big thickness differences, the contour of that bottom was consistent from part to part. As stated above, sidewall thickness consistency as measured around the central axis of the container is what Applicant has found to significantly improve thermal efficiency of the vials, especially for lyophilization.

Optional Vial Materials

[0066] Optionally, vessels, e.g., vials according to any embodiment of the invention may be made from one or more (e.g., as a composite or blend) injection moldable thermoplastic materials including, but not limited to: an olefin polymer; polypropylene (PP); polyethylene (PE); cyclic olefin copolymer (COC); cyclic olefin polymer (COP); polymethylpentene; polyester; polyethylene terephthalate; polyethylene naphthalate; polybutylene terephthalate (PBT); PVdC (polyvinylidene chloride); polyvinyl chloride (PVC); polycarbonate; polymethylmethacrylate; polylactic acid; polylactic acid; polystyrene; hydrogenated polystyrene; poly(cyclohexylethylene) (PCHE); nylon; polyurethane polyacrylonitrile; polyacrylonitrile (PAN); an ionomeric resin; Surlyn® ionomeric resin. For applications in which clear and glass-like polymers are desired, a cyclic olefin polymer (COP), cyclic olefin copolymer (COC) or polycarbonate may be preferred. Such materials may be manufactured, e.g., by injection molding or injection stretch blow molding, to very tight and precise tolerances (generally much tighter than achievable with glass).

[0067] Preferably, the material is an amorphous polymer, such as a cyclic olefin polymer (COP), instead of a crystalline material. Amorphous polymers can be defined as polymers that do not exhibit any crystalline structures in X-ray or electron scattering experiments. They form a broad group of materials, including glassy, brittle and ductile polymers. Amorphous materials have no

patterned order between the molecules. Amorphous materials include atactic polymers since the molecular structure does not generally result in crystallization. Examples of these types of plastics are polystyrene, PVC and atactic polypropylene. The presence of polar groups, such as a carbonyl group CO in vinyl type polymers, also restricts crystallization. Polyvinyl acetate, all polyacrylates and polymethylacrylates are examples of carbonyl groups being present and the resulting groups being amorphous. Polyacrylonitrile is an exception to this. Even amorphous materials can have a degree of crystallinity with the formation of crystallites throughout their structure. The degree of crystallinity is an inherent characteristic of each polymer but may also be affected or controlled by processes such as polymerisation and molding.

[0068] Crystalline materials exhibit areas of highly organized and tightly packed molecules. These areas of crystallinity are called spherulites and can be varied in shape and size with amorphous areas between the crystallites. The length of polymers contributes to their ability to crystallize as the chains pack closely together, as well as overlapping and aligning the atoms of the molecules in a repeating lattice structure. Polymers with a backbone of carbon and oxygen, such as acetals, readily crystallize. Plastic materials, such as nylon and other polyamides, crystallize due to the parallel chains and strong hydrogen bonds of the carbonyl and amine groups. Polyethylene is crystalline because the chains are highly regular and easily aligned. Polytetrafluoroethylene (PTFE) is also highly symmetric with fluorine atoms replacing all the hydrogens along the carbon backbone. It, too, is highly crystalline. Isomer structures also affect the degree of crystallinity.

[0069] As the atactic stereochemistry results in amorphous polymers, those that are isotactic and syndiotactic result in crystalline structures, forming as chains align to form crystallites. These stereospecific forms or propylene are those which are preferable for structural applications due to their degree of crystallinity. The degree of crystallinity affects many polymeric properties. In turn, other characteristics and processes affect the degree of crystallinity. The higher the molecular weight, the lower the degree of crystallinity and the areas of the crystallites are more imperfect. The degree of crystallinity also depends on the time available for crystallization to occur. Processors can use this time to their advantage by quenching or annealing to control the time for crystallization to occur. Highly branched polymers tend to have lower degrees of crystallinity, as is easily seen in the difference between branched low-density polyethylene (LDPE) and the more crystalline high-density polyethylene (HDPE). LDPE is more flexible, less dense and more transparent than HDPE. This is

an excellent example that the same polymer can have varied degrees of crystallinity. Stress can also result in crystallinity as polymer chains align orienting the crystallites. Drawing fibers, the direction of extrusion and gate placements will also affect the orientation of polymers and therefore the crystallites of the material. This allows the processor to maximize the effects and benefits of the inherent crystallinity of the polymer being used in the application. Amorphous polymers have inherent characteristics desirable for the process, methods, and resulting vessels or containers of the disclosed concept, including natural heat tolerance and molding capacity, and good water barrier from or through the material.

PECVD Coating Layers

[0070] As discussed above, use of uncoated polymer vials for lyophilization may be limited due to insufficient barrier properties of the polymer material alone.

[0071] Accordingly, in another aspect, the disclosed concept optionally includes use of any embodiments (or combination of embodiments) of vials according to the disclosed concept having a PECVD coating or PECVD coating set. The vials may be made from, e.g., a thermoplastic material. Optionally, the vial according to any embodiment is made from an injection moldable thermoplastic material as defined above, in particular a material that appears clear and glass-like in final form, e.g., a cyclic olefin polymer (COP), cyclic olefin copolymer (COC) or polycarbonate. Such materials may be manufactured, e.g., by injection molding, to very tight and precise tolerances (generally much tighter than achievable with glass). This is a benefit when trying to balance the competing considerations of seal tightness and low plunger force in plunger design.

[0072] For some applications, it may be desired to provide one or more coatings or layers to the interior wall of a parenteral container to modify the properties of that container. For example, one or more coatings or layers may be added to a parenteral container, e.g., to improve the barrier properties of the container and prevent interaction between the container wall (or an underlying coating) and drug product held within the container. Such coatings or layers may be constructed in accordance with the teachings of PCT/US2014/023813, which is incorporated by reference herein in its entirety. Preferred methods of applying one or more of a barrier layer and underlying tie layer to the inner surface of a vessel (e.g., vial) is by plasma enhanced chemical vapor deposition (PECVD), such as described in, e.g., U.S. Pat. App. Pub. No. 20130291632, U.S. Pat. No. 7,985,188, and/or PCT/US2016/047622, each of which is incorporated by reference herein in its entirety.

Tri-Layer Coating Set

[0073] Optionally, in any embodiment the inner surface of a vial according to an aspect of the disclosed concept may include a coating set comprising one or more coatings or layers. The vial may optionally include at least one tie coating or layer, at least one barrier coating or layer, and at least one organo-siloxane coating or layer. The organo-siloxane coating or layer preferably has pH protective properties. This embodiment of the coating set is referred to herein as a "tri-layer coating set" in which the barrier coating or layer is protected against contents having a pH otherwise high enough to remove it by being sandwiched between the pH protective organo-siloxane coating or layer and the tie coating or layer. The contemplated thicknesses of the respective layers in nanometers (preferred ranges in parentheses) are given in the following Tri-layer Thickness Table:

Table 1

Tri-layer Thickness		
Adhesion (nm)	**Barrier (nm)**	**Protection (nm)**
5-100 (5-20)	20-200 (20-30)	50-500 (100-200)

[0074] Properties, compositions and methods for generating of each of the coatings that make up the tri-layer coating set are described in U.S. Pat. No. 9,937,099, which is incorporated-by-reference herein in its entirety.

[0075] The tie coating or layer has at least two functions. One function of the tie coating or layer is to improve adhesion of a barrier coating or layer to a substrate (*e.g.*, the inner surface of the vial), in particular a thermoplastic substrate, although a tie layer can be used to improve adhesion to a glass substrate or to another coating or layer. For example, a tie coating or layer, also referred to as an adhesion layer or coating can be applied to the substrate and the barrier layer can be applied to the adhesion layer to improve adhesion of the barrier layer or coating to the substrate.

[0076] Another function of the tie coating or layer has been discovered: a tie coating or layer applied under a barrier coating or layer can improve the function of a pH protective organo-siloxane coating or layer applied over the barrier coating or layer.

[0077] The tie coating or layer can be composed of, comprise, or consist essentially of SiOxCy, in which x is between 0.5 and 2.4 and y is between 0.6 and 3. Alternatively, the atomic ratio can be

expressed as the formula SiwOxCy. The atomic ratios of Si, O, and C in the tie coating or layer are, as several options:

Si 100 : O 50–150 : C 90-200 (i.e. w = 1, x = 0.5 to 1.5, y = 0.9 to 2);

Si 100 : O 70–130 : C 90-200 (i.e. w = 1, x = 0.7 to 1.3, y = 0.9 to 2)

Si 100 : O 80–120 : C 90-150 (i.e. w = 1, x = 0.8 to 1.2, y = 0.9 to 1.5)

Si 100 : O 90-120 : C 90-140 (i.e. w = 1, x = 0.9 to 1.2, y = 0.9 to 1.4), or

Si 100 : O 92-107 : C 116-133 (i.e. w = 1, x = 0.92 to 1.07, y = 1.16 to 1.33).

[0078] The atomic ratio can be determined by XPS. Taking into account the H atoms, which are not measured by XPS, the tie coating or layer may thus in one aspect have the formula SiwOxCyHz (or its equivalent SiOxCy), for example where w is 1, x is from about 0.5 to about 2.4, y is from about 0.6 to about 3, and z is from about 2 to about 9. Typically, a tie coating or layer would hence contain 36% to 41% carbon normalized to 100% carbon plus oxygen plus silicon.

[0079] The barrier coating or layer for any embodiment defined in this specification (unless otherwise specified in a particular instance) is a coating or layer, optionally applied by PECVD as indicated in U.S. Pat. No. 7,985,188. The barrier coating preferably is characterized as a "SiOx" coating, in which x, the ratio of oxygen to silicon atoms, is from about 1.5 to about 2.9. The thickness of the SiOx or other barrier coating or layer can be measured, for example, by transmission electron microscopy (TEM), and its composition can be measured by X-ray photoelectron spectroscopy (XPS). The barrier layer is effective to prevent oxygen, carbon dioxide, water vapor, or other gases (e.g. residual monomers of the polymer from which the container wall is made) from entering the container and/or to prevent leaching of the pharmaceutical material into or through the container wall.

[0080] The Applicant has found that barrier layers or coatings of SiOx are eroded or dissolved by some fluids, for example aqueous compositions having a pH above about 5. Since coatings applied by chemical vapor deposition can be very thin – tens to hundreds of nanometers thick – even a relatively slow rate of erosion can remove or reduce the effectiveness of the barrier layer in less time than the desired shelf life of a product package. This is particularly a problem for fluid pharmaceutical compositions, since many of them have a pH of roughly 7, or more broadly in the range of 5 to 9, similar to the pH of blood and other human or animal fluids. The higher the pH of the pharmaceutical preparation, the more quickly it erodes or dissolves the SiOx coating. Optionally,

this problem can be addressed by protecting the barrier coating or layer, or other pH sensitive material, with a pH protective organo-siloxane coating or layer.

[0081] Optionally, the pH protective coating or layer can be composed of, comprise, or consist essentially of SiwOxCyHz (or its equivalent SiOxCy) or SiwNxCyHz or its equivalent SiNxCy). The atomic ratio of Si : O : C or Si : N : C can be determined by XPS (X-ray photoelectron spectroscopy). Taking into account the H atoms, the pH protective coating or layer may thus in one aspect have the formula SiwOxCyHz, or its equivalent SiOxCy, for example where w is 1, x is from about 0.5 to about 2.4, y is from about 0.6 to about 3, and z is from about 2 to about 9.

[0082] Typically, expressed as the formula SiwOxCy, the atomic ratios of Si, O, and C are, as several options:

Si 100 : O 50–150 : C 90-200 (i.e. w = 1, x = 0.5 to 1.5, y = 0.9 to 2);

Si 100 : O 70–130 : C 90-200 (i.e. w = 1, x = 0.7 to 1.3, y = 0.9 to 2)

Si 100 : O 80–120 : C 90-150 (i.e. w = 1, x = 0.8 to 1.2, y = 0.9 to 1.5)

Si 100 : O 90-120 : C 90-140 (i.e. w = 1, x = 0.9 to 1.2, y = 0.9 to 1.4)

Si 100 : O 92-107 : C 116-133 (i.e. w = 1, x = 0.92 to 1.07, y = 1.16 to 1.33) ,

or

Si 100 : O 80–130 : C 90-150.

[0083] Alternatively, the organo-siloxane coating or layer can have atomic concentrations normalized to 100% carbon, oxygen, and silicon, as determined by X-ray photoelectron spectroscopy (XPS) of less than 50% carbon and more than 25% silicon. Alternatively, the atomic concentrations are from 25 to 45% carbon, 25 to 65% silicon, and 10 to 35% oxygen. Alternatively, the atomic concentrations are from 30 to 40% carbon, 32 to 52% silicon, and 20 to 27% oxygen. Alternatively, the atomic concentrations are from 33 to 37% carbon, 37 to 47% silicon, and 22 to 26% oxygen.

[0084] Optionally, the atomic concentration of carbon in the pH protective coating or layer, normalized to 100% of carbon, oxygen, and silicon, as determined by X-ray photoelectron spectroscopy (XPS), can be greater than the atomic concentration of carbon in the atomic formula for the organosilicon precursor. For example, embodiments are contemplated in which the atomic concentration of carbon increases by from 1 to 80 atomic percent, alternatively from 10 to 70 atomic percent, alternatively from 20 to 60 atomic percent, alternatively from 30 to 50 atomic percent, alternatively from 35 to 45 atomic percent, alternatively from 37 to 41 atomic percent.

[0085] Optionally, the atomic ratio of carbon to oxygen in the pH protective coating or layer can be increased in comparison to the organosilicon precursor, and/or the atomic ratio of oxygen to silicon can be decreased in comparison to the organosilicon precursor.

[0086] An exemplary empirical composition for a pH protective coating according to an optional embodiment is $SiO_{1.3}C_{0.8}H_{3.6}$.

[0087] Optionally in any embodiment, the pH protective coating or layer comprises, consists essentially of, or consists of PECVD applied coating.

[0088] Optionally in any embodiment, the pH protective coating or layer is applied by employing a precursor comprising, consisting essentially of, or consisting of a silane. Optionally in any embodiment, the silane precursor comprises, consists essentially of, or consists of any one or more of an acyclic or cyclic silane, optionally comprising, consisting essentially of, or consisting of any one or more of silane, trimethylsilane, tetramethylsilane, Si2–Si4 silanes, triethyl silane, tetraethyl silane, tetrapropylsilane, tetrabutylsilane, or octamethylcyclotetrasilane, or tetramethylcyclotetrasilane.

[0089] Optionally in any embodiment, the pH protective coating or layer comprises, consists essentially of, or consists of PECVD applied amorphous or diamond-like carbon. Optionally in any embodiment, the amorphous or diamond-like carbon is applied using a hydrocarbon precursor. Optionally in any embodiment, the hydrocarbon precursor comprises, consists essentially of, or consists of a linear, branched, or cyclic alkane, alkene, alkadiene, or alkyne that is saturated or unsaturated, for example acetylene, methane, ethane, ethylene, propane, propylene, n-butane, i-butane, butane, propyne, butyne, cyclopropane, cyclobutane, cyclohexane, cyclohexene, cyclopentadiene, or a combination of two or more of these. Optionally in any embodiment, the amorphous or diamond-like carbon coating has a hydrogen atomic percent of from 0.1% to 40%, alternatively from 0.5% to 10%, alternatively from 1% to 2%, alternatively from 1.1 to 1.8%

[0090] Optionally in any embodiment, the pH protective coating or layer comprises, consists essentially of, or consists of PECVD applied SiN. Optionally in any embodiment, the PECVD applied SiN is applied using a silane and a nitrogen-containing compound as precursors. Optionally in any embodiment, the silane is an acyclic or cyclic silane, optionally comprising, consisting essentially of, or consisting of silane, trimethylsilane, tetramethylsilane, Si2–Si4 silanes, triethylsilane, tetraethylsilane, tetrapropylsilane, tetrabutylsilane, octamethylcyclotetrasilane, or a combination of two or more of these. Optionally in any embodiment, the nitrogen-containing

compound comprises, consists essentially of, or consists of any one or more of: nitrogen gas, nitrous oxide, ammonia or a silazane. Optionally in any embodiment, the silazane comprises, consists essentially of, or consists of a linear silazane, for example hexamethylene disilazane (HMDZ), a monocyclic silazane, a polycyclic silazane, a polysilsesquiazane, or a combination of two or more of these.

[0091] Optionally in any embodiment, the PECVD for the pH protective coating or layer is carried out in the substantial absence or complete absence of an oxidizing gas. Optionally in any embodiment, the PECVD for the pH protective coating or layer is carried out in the substantial absence or complete absence of a carrier gas.

[0092] Optionally an FTIR absorbance spectrum of the pH protective coating or layer SiOxCyHz has a ratio greater than 0.75 between the maximum amplitude of the Si-O-Si symmetrical stretch peak normally located between about 1000 and 1040 cm-1, and the maximum amplitude of the Si-O-Si asymmetric stretch peak normally located between about 1060 and about 1100 cm-1. Alternatively in any embodiment, this ratio can be at least 0.8, or at least 0.9, or at least 1.0, or at least 1.1, or at least 1.2. Alternatively in any embodiment, this ratio can be at most 1.7, or at most 1.6, or at most 1.5, or at most 1.4, or at most 1.3. Any minimum ratio stated here can be combined with any maximum ratio stated here, as an alternative embodiment.

[0093] Optionally, in any embodiment the pH protective coating or layer, in the absence of the liquid filling, has a non-oily appearance. This appearance has been observed in some instances to distinguish an effective pH protective coating or layer from a lubricity layer (e.g., as described in U.S. Pat. No. 7,985,188), which in some instances has been observed to have an oily (i.e. shiny) appearance.

[0094] The pH protective coating or layer optionally can be applied by plasma enhanced chemical vapor deposition (PECVD) of a precursor feed comprising an acyclic siloxane, a monocyclic siloxane, a polycyclic siloxane, a polysilsesquioxane, a monocyclic silazane, a polycyclic silazane, a polysilsesquiazane, a silatrane, a silquasilatrane, a silproatrane, an azasilatrane, an azasilquasiatrane, an azasilproatrane, or a combination of any two or more of these precursors. Some particular, non-limiting precursors contemplated for such use include octamethylcyclotetrasiloxane (OMCTS).

[0095] Other precursors and methods can be used to apply the pH protective coating or layer or

passivating treatment. For example, hexamethylene disilazane (HMDZ) can be used as the precursor. HMDZ has the advantage of containing no oxygen in its molecular structure. This passivation treatment is contemplated to be a surface treatment of the SiOx barrier layer with HMDZ. To slow down and/or eliminate the decomposition of the silicon dioxide coatings at silanol bonding sites, the coating must be passivated. It is contemplated that passivation of the surface with HMDZ (and optionally application of a few mono layers of the HMDZ-derived coating) will result in a toughening of the surface against dissolution, resulting in reduced decomposition. It is contemplated that HMDZ will react with the -OH sites that are present in the silicon dioxide coating, resulting in the evolution of NH_3 and bonding of S-$(CH_3)_3$ to the silicon (it is contemplated that hydrogen atoms will be evolved and bond with nitrogen from the HMDZ to produce NH_3).

[0096] Another way of applying the pH protective coating or layer is to apply as the pH protective coating or layer an amorphous carbon or fluorocarbon coating, or a combination of the two.

[0097] Amorphous carbon coatings can be formed by PECVD using a saturated hydrocarbon, (e.g. methane or propane) or an unsaturated hydrocarbon (e.g. ethylene, acetylene) as a precursor for plasma polymerization. Fluorocarbon coatings can be derived from fluorocarbons (for example, hexafluoroethylene or tetrafluoroethylene). Either type of coating, or a combination of both, can be deposited by vacuum PECVD or atmospheric pressure PECVD. It is contemplated that that an amorphous carbon and/or fluorocarbon coating will provide better passivation of an SiOx barrier layer than a siloxane coating since an amorphous carbon and/or fluorocarbon coating will not contain silanol bonds.

[0098] It is further contemplated that fluorosilicon precursors can be used to provide a pH protective coating or layer over a SiOx barrier layer. This can be carried out by using as a precursor a fluorinated silane precursor such as hexafluorosilane and a PECVD process. The resulting coating would also be expected to be a non-wetting coating.

[0099] Yet another coating modality contemplated for protecting or passivating a SiOx barrier layer is coating the barrier layer using a polyamidoamine epichlorohydrin resin. For example, the barrier coated part can be dip coated in a fluid polyamidoamine epichlorohydrin resin melt, solution or dispersion and cured by autoclaving or other heating at a temperature between 60 and 100°C. It is contemplated that a coating of polyamidoamine epichlorohydrin resin can be preferentially used in

aqueous environments between pH 5-8, as such resins are known to provide high wet strength in paper in that pH range. Wet strength is the ability to maintain mechanical strength of paper subjected to complete water soaking for extended periods of time, so it is contemplated that a coating of polyamidoamine epichlorohydrin resin on a SiOx barrier layer will have similar resistance to dissolution in aqueous media. It is also contemplated that, because polyamidoamine epichlorohydrin resin imparts a lubricity improvement to paper, it will also provide lubricity in the form of a coating on a thermoplastic surface made of, for example, COC or COP.

[00100] Even another approach for protecting a SiOx layer is to apply as a pH protective coating or layer a liquid-applied coating of a polyfluoroalkyl ether, followed by atmospheric plasma curing the pH protective coating or layer. For example, it is contemplated that the process practiced under the trademark TriboGlide® can be used to provide a pH protective coating or layer that also provides lubricity.

[00101] Thus, a pH protective coating for a thermoplastic vessel wall according to an aspect of the invention may comprise, consist essentially of, or consist of any one of the following: plasma enhanced chemical vapor deposition (PECVD) applied coating having the formula $SiO_xC_yH_z$, in which x is from 0 to 0.5, alternatively from 0 to 0.49, alternatively from 0 to 0.25 as measured by X ray photoelectron spectroscopy (XPS), y is from about 0.5 to about 1.5, alternatively from about 0.8 to about 1.2, alternatively about 1, as measured by XPS, and z is from 0 to 2 as measured by Rutherford Backscattering Spectrometry (RBS), alternatively by Hydrogen Forward Scattering Spectrometry (HFS); or PECVD applied amorphous or diamond-like carbon, CH_z, in which z is from 0 to 0.7, alternatively from 0.005 to 0.1, alternatively from 0.01 to 0.02; or PECVD applied SiN_b, in which b is from about 0.5 to about 2.1, alternatively from about 0.9 to about 1.6, alternatively from about 1.2 to about 1.4, as measured by XPS.

[00102] Optionally, in any embodiment, a top surface treatment or coating is applied atop the pH protective layer to optimize the compatibility of the vial surface with specific drugs. Such surface treatment or coating eliminates liquid hang-up on the vial walls that may cause small amounts of the drug to be lyophilized on the wall, which is unattractive and may result in rejected product.

PECVD Apparatus

[00103] PECVD apparatus suitable for applying any of the PECVD coatings or layers described in this specification, including the tie coating or layer, the barrier coating or layer or the organo-

siloxane coating or layer, are shown and described in U.S. Pat. No. 7,985,188 and U.S. Pat. App. Pub. No. 20130291632. This apparatus optionally includes a vessel holder, an inner electrode, an outer electrode, and a power supply. A vessel seated on the vessel holder defines a plasma reaction chamber, optionally serving as its own vacuum chamber. Optionally, a source of vacuum, a reactant gas source, a gas feed or a combination of two or more of these can be supplied. Optionally, a gas drain, not necessarily including a source of vacuum, is provided to transfer gas to or from the interior of a vessel seated on the port to define a closed chamber. Additional details of optional PECVD apparatus and use of the same to apply coatings follows, with reference to Fig. 7.

[00104] A PECVD apparatus or coating station 1060 suitable for the present purpose includes a vessel holder 1050, an inner electrode defined by the probe 1108, an outer electrode 1160, and a power supply 1162. The pre-assembly 1012 seated on the vessel holder 1050 defines a plasma reaction chamber, which optionally can be a vacuum chamber. Optionally, a source of vacuum 1098, a reactant gas source 1144, a gas feed (probe 1108) or a combination of two or more of these can be supplied.

[00105] The PECVD apparatus can be used for atmospheric-pressure PECVD, in which case the plasma reaction chamber defined by the pre-assembly 1012 does not need to function as a vacuum chamber.

[00106] The vessel holder 1050 comprises a gas inlet port for conveying a gas into the pre-assembly 1012 seated on the opening. The gas inlet port can have a sliding seal provided for example by at least one O-ring, or two O- rings in series, or three O-rings in series, which can seat against a cylindrical probe 1108 when the probe 1108 is inserted through the gas inlet port. The probe 1108 can be a gas inlet conduit that extends to a gas delivery port at its distal end 1110. The distal end 1110 of the illustrated embodiment can be inserted at an appropriate depth in the pre-assembly 1012 for providing one or more PECVD reactants and other precursor feed or process gases.

[00107] FIG. 7 shows additional optional details of the coating station 1060 that are usable, for example, with all the illustrated embodiments. The coating station 1060 can also have a main vacuum valve 1574 in its vacuum line 1576 leading to the pressure sensor 1152. A manual bypass valve 1578 can be provided in the bypass line 1580. A vent valve 1582 controls flow at the vent 1404.

[00108] Flow out of the PECVD gas or precursor source 1144 can be controlled by a main

reactant gas valve 1584 regulating flow through the main reactant feed line 1586. One component of the gas source 1144 can be the organosilicon liquid reservoir 1588, containing the precursor. The contents of the reservoir 1588 can be drawn through the organosilicon capillary line 1590, which optionally can be provided at a suitable length to provide the desired flow rate. Flow of organosilicon vapor can be controlled by the organosilicon shut-off valve 1592. Pressure can be applied to the headspace 1614 of the liquid reservoir 1588, for example a pressure in the range of 0-15 psi (0 to 78 cm. Hg), from a pressure source 1616 such as pressurized air connected to the headspace 1614 by a pressure line 1618 to establish repeatable organosilicon liquid delivery that is not dependent on atmospheric pressure (and the fluctuations therein). The reservoir 1588 can be sealed and the capillary connection 1620 can be at the bottom of the reservoir 1588 to ensure that only neat organosilicon liquid (not the pressurized gas from the headspace 1614) flows through the capillary tube 1590. The organosilicon liquid optionally can be heated above ambient temperature, if necessary or desirable to cause the organosilicon liquid to evaporate, forming an organosilicon vapor. To accomplish this heating, the apparatus can advantageously include heated delivery lines from the exit of the precursor reservoir to as close as possible to the gas inlet into the vessel. Preheating can be useful, for example, when feeding OMCTS.

[00109] Oxidant gas can be provided from the oxidant gas tank 1594 via an oxidant gas feed line 1596 controlled by a mass flow controller 1598 and provided with an oxidant shut-off valve 1600.

[00110] Optionally in any embodiment, other precursor, oxidant, and/or carrier gas reservoirs such as 1602 can be provided to supply additional materials if needed for a particular deposition process. Each such reservoir such as 1602 can have an appropriate feed line 1604 and shut-off valve 1606.

[00111] The processing station 1060 can include an electrode 1160 fed by a radio frequency power supply 1162 for providing an electric field for generating plasma within the pre-assembly 1012 during processing. In this embodiment, the probe 1108 can be electrically conductive and can be grounded, thus providing a counter-electrode within the pre-assembly 1012. Alternatively, in any embodiment the outer electrode 1160 can be grounded and the probe 1108 can be directly connected to the power supply 1162.

[00112] The outer electrode 1160 can either be generally cylindrical or a generally U-shaped elongated channel. Each embodiment can have one or more sidewalls and optionally a top end 1168, disposed about the pre-assembly 1012 in close proximity.

[00113] Accordingly, in one optional aspect, the invention may incorporate an organo-siloxane coating on the inner surface of a container which may, for example, be any embodiment of the pH protective coating discussed above. The organo-siloxane coating may be applied directly to the interior wall of the container or as a top layer on a multi-layer coating set, *e.g.*, the tri-layer coating set discussed above.

[00114] The organo-siloxane coating can optionally provide multiple functions: (1) a pH resistant layer that protects an underlying layer or underlying polymer substrate from drug products having a pH from 4-10, optionally from 5-9; (2) a drug contact surface that minimizes aggregation, extractables and leaching; and (3) in the case of a protein-based drug, reduced protein binding on the container surface.

[00115] In one embodiment, the tie or adhesion coating or layer and the barrier coating or layer, and optionally the pH protective layer, are applied in the same apparatus, without breaking vacuum between the application of the adhesion coating or layer and the barrier coating or layer or, optionally, between the barrier coating or layer and the pH protective coating or layer. During the process, a partial vacuum is drawn in the lumen. While maintaining the partial vacuum unbroken in the lumen, a tie coating or layer of SiOxCy is applied by a tie PECVD coating process. The tie PECVD coating process is carried out by applying sufficient power to generate plasma within the lumen while feeding a gas suitable for forming the coating. The gas feed includes a linear siloxane precursor, optionally oxygen, and optionally an inert gas diluent. The values of x and y are as determined by X-ray photoelectron spectroscopy (XPS). Then, while maintaining the partial vacuum unbroken in the lumen, the plasma is extinguished. A tie coating or layer of SiOxCy, for which x is from about 0.5 to about 2.4 and y is from about 0.6 to about 3, is produced on the inside surface as a result.

[00116] Later during the process, while maintaining the partial vacuum unbroken in the lumen, a barrier coating or layer is applied by a barrier PECVD coating process. The barrier PECVD coating process is carried out by applying sufficient power to generate plasma within the lumen while feeding a gas. The gas feed includes a linear siloxane precursor and oxygen. A barrier coating or layer of SiOx, wherein x is from 1.5 to 2.9 as determined by XPS is produced between the tie coating or layer and the lumen as a result.

[00117] Then optionally, while maintaining the partial vacuum unbroken in the lumen, the plasma

is extinguished.

[00118] Later, as a further option, a pH protective coating or layer of SiOxCy can be applied. In this formula as well, x is from about 0.5 to about 2.4 and y is from about 0.6 to about 3, each as determined by XPS. The pH protective coating or layer is optionally applied between the barrier coating or layer and the lumen, by a pH protective PECVD coating process. This process includes applying sufficient power to generate plasma within the lumen while feeding a gas including a linear siloxane precursor, optionally oxygen, and optionally an inert gas diluent.

[00119] Then optionally, while maintaining the partial vacuum unbroken in the lumen, the plasma is extinguished.

[00120] Later, as a further option, a lubricity coating or layer of SiOxCy can be applied. In this formula as well, x is from about 0.5 to about 2.4 and y is from about 0.6 to about 3, each as determined by XPS. The lubricity coating or layer is optionally applied on top of the pH protective coating, by a lubricity PECVD coating process. This process includes applying sufficient power to generate plasma within the lumen while feeding a gas including an organo siloxane precursor, optionally oxygen, and optionally an inert gas diluent.

[00121] Optionally in any embodiment, the PECVD process for applying the tie coating or layer, the barrier coating or layer, and/or the pH protective coating or layer, and/or the lubricty coating or any combination of two or more of these, is carried out by applying pulsed power (alternatively the same concept is referred to in this specification as "energy") to generate plasma within the lumen.

[00122] Alternatively, the tie PECVD coating process, or the barrier PECVD coating process, or the pH protective PECVD coating process, or any combination of two or more of these, can be carried out by applying continuous power to generate plasma within the lumen.

[00123] The trilayer coating as described in this embodiment is applied by adjusting the flows of a single organosilicon monomer (HMDSO) and oxygen and also varying the PECVD generating power between each layer (without breaking vacuum between any two layers).

[00124] The vessel (e.g., a COC or COP vial) is placed on a vessel holder, sealed, and a vacuum is pulled within the vessel. After pulling vacuum, the gas feed of precursor, oxygen, and argon is introduced, then at the end of the "plasma delay" continuous (i.e. not pulsed) RF power at 13.56 MHz is turned on to form the tie coating or layer. Then power is turned off, gas flows are adjusted, and after the plasma delay power is turned on for the second layer -- an SiOx barrier coating or layer.

This is then repeated for a third layer before the gases are cut off, the vacuum seal is broken, and the vessel is removed from the vessel holder. The layers are put down in the order of Tie then Barrier then pH Protective. An exemplary process settings are as shown in the following table:

Table 2

Coating	O2 (sccm)	Ar (sccm)	HMDSO (sccm)	Power (W)	Deposition Time (sec)
Tie	1	40	2	20	2.5
Barrier	100	0	1	60	15
pH Protective	1	40	2	20	10

[00125] As a still a still further alternative, pulsed power can be used for some steps, and continuous power can be used for others. For example, when preparing a trilayer coating or layer composed of a tie coating or layer, a barrier coating or layer, and a pH protective coating or layer, an option specifically contemplated for the tie PECVD coating process and for the pH protective PECVD coating process is pulsed power, and an option contemplated for the corresponding barrier layer is using continuous power to generate plasma within the lumen.

PECVD Water Barrier Coating or Layer

[00126] Optionally, in any embodiment, the vial may include deposited thereon a PECVD water barrier coating or layer, as described in Applicant's WO 2019/191269, which is incorporated by reference herein in its entirety. Such a water barrier layer is particularly helpful to provide necessary barrier properties for vials made from cyclic olefin copolymers (COC) or cyclic olefin polymers (COP). COC and COP are amorphous polyolefins, so they are transparent. While COP/COC generally have good water barrier properties for thermoplastics, they may not have sufficient water barrier properties for storing lyophilized drugs, which are supersensitive to moisture.

[00127] Optionally, in any embodiment, the vial may include a PECVD water barrier layer in addition to or as an alternative to the above-described tri-layer coating set. Optionally, in any embodiment, the vial may include a PECVD water barrier layer in addition to any one or more of the individual layers of the above-described tri-layer coating set.

[00128] The PECVD water barrier layer has a water contact angle from 80 to 180 degrees, optionally from larger than 80 degrees to less than 180 degrees, optionally from 90 degrees to 160 degrees, optionally from 100 degrees to 150 degrees, optionally from 110 degrees to 150 degrees,

applied to a surface of the vial using a water barrier coating or layer precursor. The precursor comprises as least one of a saturated or unsaturated, linear or cyclic aliphatic fluorocarbon precursor having from 1 to 10, optionally 1 to 6, optionally 2 to 6 carbon atoms and from 4 to 20 fluorine atoms per molecule, optionally hexafluropropylene (C_3F_6), octafluorocyclobutane (C_4F_8), tetrafluoroethylene (C_2F_4), hexafluoroethane (C_2F_6), hexafluoropropylene (C_3F_6), octafluorocyclobutane (C_4F_8), perfluorohexane (C_6F_{14}), perfluoro-2-methyl-2-pentene (C_6F_{12}). The precursor further comprises a saturated or unsaturated hydrocarbon having from 1 to 6 carbon atoms, for example lower alkanes having from 1 to 4 carbon atoms, alkenes or alkynes having from 2 to 4 carbon atoms, for example acetylene (C_2H_2) or methane (CH_4), optionally acetylene (C_2H_2), a saturated or unsaturated hydrofluorocarbon having from 1 to 6 carbon atoms; or any combination thereof.

[00129] Optionally, in any embodiment, the water barrier layer is between the tri-layer coating and the interior surface of the vessel wall. Optionally, in any embodiment, the water barrier layer is deposited directly to the polymer interior surface of the vessel or vial.

[00130] An optional method for applying the water barrier layer and optionally additional coatings (e.g., tie layer, barrier layer and/or pH protective layer) is now described. The method includes at least partially evacuating a region adjacent to a surface of the vessel wall, forming a partially evacuated region. The method further includes feeding the water barrier coating or layer precursor to the partially evacuated region and generating a plasma in the partially evacuated region, forming a water barrier layer supported by the wall adjacent to the evacuated region. The method further includes, before or after the step of feeding the water barrier layer precursor, feeding a precursor gas for a first coating or layer of the tri-layer coating set to the partially evacuated region and generating plasma in the partially evacuated region, forming a coating or layer of the tri-layer coating set supported by the wall adjacent to the evacuated region. Optionally, the method further includes, after feeding a precursor gas for a first coating of the tri-layer coating set, feeding a precursor gas for a second coating of the tri-layer coating set to the partially evacuated region and generating plasma in the partially evacuated region, forming a second coating or layer of the gas barrier coating set supported by the wall adjacent to the evacuated region. Optionally, between at least two or three of the feeding steps, the vacuum in the evacuated region is not broken.

[00131] Optionally, the water barrier coating or layer is from 1 nm to 500 nm thick, optionally

from 1 nm to 300 nm thick, optionally from 1 nm to 100 nm thick, optionally from 10 nm to 300 nm thick, optionally from 50 nm to 300 nm thick, optionally from 50 nm to 200 nm thick.

[00132] Optionally, in any embodiment, the water barrier coating or layer is in direct contact with the vessel (or vial) wall, optionally the inner surface and/or outer surface of the wall.

[00133] Optionally, in any embodiment, the water barrier coating or layer is deposited atop a tri-layer coating set on an interior surface of the vial. Optionally, in any embodiment, the tri-layer coating set is deposited atop the water barrier coating or layer on an interior surface of the vial. Optionally, in any embodiment, the vial includes a water barrier layer with no tri-layer coating set. Optionally, in any embodiment, the vial includes a tri-layer coating set with no water barrier layer.

[00134] Optionally, for the water barrier coating applied using fluorocarbons as the precursors, the typical coating process conditions are as follows:

- Power frequency 13.56 MHz;
- Precursor: Hexafluoropropylene (C_3F_6) or Octafluorocyclobutane (C_4F_8);
- Gas flow rate: 5-10 sccm;
- Carrier gas flow rate: 2-10 sccm;
- Base pressure 20-300 mTorr;
- Coating Pressure: 80 -900 mTorr;
- Coating time: 5-30 s.

[00135] Optionally, for the water barrier coating applied using hydrocarbons as the precursors, the typical coating process conditions are as follows:

- Power frequency 13.56 MHz;
- Precursor: Acetylene (C_2H_2);
- Gas flow rate 1-10 sccm;
- Carrier gas flow rate: 2-5 sccm;
- Base pressure 20-300 mTorr;
- Coating Pressure: 80 -900 mTorr;
- Coating time: 5-30 s.

[00136] An advantage of the water barrier layer on a plastic (e.g., COC or COP) vial is that the layer significantly prevents the ingress of moisture during the shelf life (e.g., two years) in which a lyophilized drug may be stored at room temperature in the vial. The lyophilized drug is

supersensitive to water and thus the water barrier layer may be utilized to prevent the drug from absorbing moisture.

[00137] Various aspects of the invention will be illustrated in more detail with reference to the following Examples, but it should be understood that the present invention is not deemed to be limited thereto.

EXAMPLES

Example 1

Heat Transfer Variation in COP Vials Made According to Inventive Method Versus Glass Vials

[00138] In this example, heat transfer variation of standard glass vials by Schott GmbH was compared with that of Applicant's substantially flat bottomed coated COP 10 mL vials. The glass vials had a configuration substantially similar to the prior art vial 10 of Fig. 1. This example demonstrates that such variation is significantly lower for COP vials made in accordance with optional aspects of the disclosed concept than standard glass vials. This difference is attributable to lower variation in mass, density, wall thickness and flatness of the base of the COP vials according to an optional aspect of the disclosed concept, compared to the standard glass vials. The practical effect is much more consistent drying rates during lyophilization for Applicant's substantially flat bottomed COP vials compared to standard glass vials.

[00139] The heat transfer coefficient of vials (Kv) is dependent on wall thickness and mass of the vial. Material properties (e.g., thermal conductivity) may impact this as well. The contour or flatness of the vial base and contact of the base with the shelf (standing surface during lyophilization) is also impactful on the thermal efficiency. A standard vial, from Schott GmbH, was compared with flat bottom COP vials made in accordance with optional embodiments of the disclosed concept. It was concluded, based on results achieved, that the substantially flat bottomed vials improved heat transfer during lyophilization. Better heat transfer enables the better lyophilization cycle times compared to glass vials. More consistent heat transfer could also be achieved due to more consistent mass and density across a batch of vials.

[00140] The glass vials had a mass of 11.708 g, ± 0.085 g. Applicant's substantially flat bottomed coated COP vials had a mass of 6.726 ± 0.005 g. Thus, Applicant's vials had a significantly more consistent mass across the batch than the glass vials. This improved mass consistency helped to provide more consistent heat transfer for lyophilization in Applicant's vials.

[00141] Consistency in vial side wall thickness, radially 360° around, as opposed to from top to bottom along the central axis, is another metric that affects thermal efficiency. Applicant's coated COP flat bottomed vial outer diameters were measured in this way and compared with the glass vials. The results of these measurement comparisons are provided in Fig. 8. As the data show, the glass vials had five times more variation in outer diameter than Applicant's COP vials.

[00142] Kv, as used in this study, is mathematically represented as follows.

$$Kv = \frac{\Delta Hsub * \dot{m}}{Area * (Tshelf - Tbottom)}$$

Where: ΔHsub = 660 cal/g (obtained from Pikal 1983 article)

$A = \pi(\frac{d}{2})^2$ and d = 24mm, which is the outer diameter of the vial bottom

T_{shelf} = -5°C

$\dot{m} = \frac{(mass\ of\ vial+water\ before\ cycle)-(mass\ of\ vial+ice\ after\ cycle)}{time\ spent\ in\ vacuum}$

T_{bottom} = unknown - measure experimentally with thermocouple.

[00143] The Kv of several flat bottomed coated COP vials was measured against that of several Schott glass vials. Results of these measurements are shown in the following table.

Table 3

Vial Type	Kv *10^4 (cal/s/cm^2/°C)	Standard Deviation
Glass	4.23	± 0.19
Coated COP (Flat Bottom)	3.56	± 0.07

[00144] Fig. 9 graphically represents the parameters under which medication in the vials was lyophilized in this study. The following table compares data between the two types of vials relating to water lost during lyophilization.

Table 4 – Relative Standard Deviation in % Water Lost at Time Points During Primary Drying Cycle

Vial Type	After 18 hrs	After 23 hrs
Glass	6.5	0.2
Coated COP (Flat Bottom)	1.7	0.5

[00145] This comparative study shows more consistent heat transfer in the coated flat bottomed COP vial batches compared to the standard glass vials. More consistent drying rates within a COP vial batch compared to glass were also found. A pharmaceutical formulation having the following components was stored in each type of vial for comparison: 1 mg/ml IVIg, 10mM glycine, 5% w/v sucrose and 0.02% v/v polysorbate 20. Residual cake moisture content was 0.62 ± 0.09% in the glass vials and 0.63 ± 0.07% in the silica-coated COP vials. Residual moisture content (<1%), cake appearance, reconstitution time, and monomeric protein recovery were similar for lyophilized formulations in both types of vials. The differences were observed in particle levels in formulations lyophilized within silica-coated flat bottomed COP vials compared to glass vials. The coated COP vials, in accordance with optional embodiments of the disclosed concept, in comparison with the borosilicate glass vials, provide the following characteristics: facilitate more consistent heat transfer and drying rates due to vial mass consistency within a batch; accommodate the same overall cycle time for lyophilization; and produce similar cake quality, reconstitution time, monomeric protein recovery and no wall residue.

[00146] While the invention has been described in detail and with reference to specific examples thereof, it will be apparent to one skilled in the art that various changes and modifications can be made therein without departing from the spirit and scope thereof.

CLAIMS

WHAT IS CLAIMED IS:

1. A polymer vial comprising a base having a base surface area, a sidewall extending up from the base, the base and sidewall defining an interior configured to house product, the sidewall narrowing at an upper section of the vial to form a neck leading to an opening that provides access to the interior, the vial being optionally round and symmetrical about a central axis, a lower portion of the sidewall comprising a first surface that is outwardly curved along a first radius having an imaginary center positioned within the vial, wherein the base is positioned below the first surface and is substantially flat such that at least 80% of the base surface area, optionally at least 85% of the base surface area, optionally at least 90% of the base surface area, comprises a standing base surface occupying a single plane.

2. The polymer vial of claim 1, wherein the base in its entirety is positioned below the first surface.

3. The polymer vial of claim 1 or 2, further comprising a second surface that extends from and is positioned below the first surface, the second surface being inwardly curved along a second radius having an imaginary center positioned outside of the vial, the second surface terminating at a peripheral edge of the base from which the standing base surface extends inwardly towards the central axis, the standing base being configured to contact and rest on a flat support surface so as to orient the vial in an upright position.

4. The polymer vial of any previous claim, wherein the vial is produced by an injection stretch blow molding process.

5. The polymer vial of any previous claim wherein the vial is made from an olefin polymer or copolymer, optionally cyclic olefin polymer or cyclic olefin copolymer.

6. The polymer vial of any previous claim comprising a PECVD water barrier coating or layer having a water contact angle of from 80 to 180 degrees, optionally from larger than 80 degrees to less than 180 degrees, optionally from 90 degrees to 160 degrees, optionally from 100 degrees to 150 degrees, optionally from 110 degrees to 150 degrees, optionally wherein the PECVD water barrier coating or layer is deposited on an interior surface or exterior surface of the vial.

7. The polymer vial of claim 6, wherein the PECVD water barrier coating or layer is applied through a process comprising: in a PECVD apparatus, supplying a water barrier coating or layer precursor to the vial and creating a plasma using the same, the water barrier coating or layer precursor comprising as least one of a saturated or unsaturated, linear or cyclic aliphatic fluorocarbon precursor having from 1 to 10, optionally 1 to 6, optionally 2 to 6 carbon atoms and from 4 to 20 fluorine atoms per molecule, optionally hexafluropropylene (C_3F_6), octafluorocyclobutane (C_4F_8), tetrafluoroethylene (C_2F_4), hexafluoroethane (C_2F_6), hexafluoropropylene (C_3F_6), octafluorocyclobutane (C_4F_8), perfluorohexane (C_6F_{14}) or perfluoro-2-methyl-2-pentene (C_6F_{12}), the water barrier coating or layer precursor further comprising a saturated or unsaturated hydrocarbon having from 1 to 6 carbon atoms, for example lower alkanes having from 1 to 4 carbon atoms, alkenes or alkynes having from 2 to 4 carbon atoms, for example acetylene (C_2H_2) or methane (CH_4), optionally acetylene (C_2H_2), a saturated or unsaturated hydrofluorocarbon having from 1 to 6 carbon atoms, or any combination thereof.

8. The polymer vial of any previous claim, optionally of claim 6 or 7, further comprising a PECVD tri-layer coating set deposited onto an interior surface of the vial, optionally wherein the PECVD tri-layer coating set is deposited atop the PECVD water barrier layer or the PECVD water barrier layer is deposited atop the PECVD tri-layer coating set.

9. The polymer vial of any previous claim further comprising a cap to fully or partially close the opening.

10. The polymer vial of any previous claim comprising drug contents stored in the interior space, wherein the drug contents optionally comprise biologic drugs, gene therapy or viral vectors.

11. A method for making a polymer vial by injection stretch blow molding, the method comprising:

a. providing a mold, the mold comprising a first mold part and a second mold part, the first mold part and second mold part being configured to meet along a central axis to form an outer shape of a sidewall of the vial, wherein respective interior sizes and configurations of the first mold part and second mold part mirror each other, the mold further comprising a base mold configured to form a base of the vial, the base mold having a substantially flat molding surface, wherein at least 80%, optionally at least 85%, optionally at least 90%, of the molding surface of the base mold occupies a single plane, the first mold part, second mold part and base mold together defining a mold cavity when the mold is in a blowing position in which the base mold is in position relative to the first and second mold parts to form the base of the vial;

b. providing a mandrel within the mold and a molten polymer preform onto the mandrel, stretching the preform with the mandrel to extend an end thereof optionally past respective molding surfaces of the first mold part and second mold part, optionally wherein the base mold is axially distal to the base mold location when the mold is in the blowing position;

c. moving the base mold axially towards the first mold part and second mold part to place the mold in the blowing position; and

d. blowing gas into the preform such that the preform expands within the molding space and conforms to respective surfaces of the first mold part, second mold part and the base mold, when the mold is in the blowing position, wherein the substantially flat molding surface of the base mold is positioned entirely axially below respective molding surfaces of the first mold part and second mold part.

12. The method of claim 11, wherein neither the first mold part nor the second mold part form any of the base of the vial.

13. The method of claim 11 or 12, wherein the base mold forms no part of the sidewall of the vial.

14. The method of any of claims 11 to 13, wherein each of the first mold part and second mold part include a first curved mold surface that leads to a second curved mold surface, the first curved mold surface following a radius with an imaginary center positioned in the mold cavity, the second curved mold surface following a radius with an imaginary center positioned outside the mold cavity.

15. The method of claim 14, wherein no portion of the substantially flat molding surface of the base mold extends axially above the second curved mold surface.

16. A polymer vial made by the method of any of claims 11 to 15, the vial comprising a base having a base surface area, a sidewall extending up from the base, the base and sidewall defining an interior configured to house product, the sidewall narrowing at an upper section of the vial to form a neck leading to an opening that provides access to the interior, the vial being optionally round and symmetrical about a central axis, a lower portion of the sidewall comprising a first surface that is outwardly curved along a first radius having an imaginary center positioned within the vial, wherein the base is positioned below the first surface and is substantially flat such that at least 80% of the base surface area, optionally at least 85% of the base surface area, optionally at least 90% of the base surface area, comprises a standing base surface occupying a single plane.

17. The polymer vial of claim 16, wherein the base in its entirety is positioned below the first surface.

18. The polymer vial of claim 16 or 17 further comprising a second surface that extends from and is positioned below the first surface, the second surface being inwardly curved along a second radius having an imaginary center positioned outside of the vial, the second surface terminating at a peripheral edge of the base from which the standing base surface extends inwardly towards the central axis, the standing base being configured to contact and rest on a flat support surface so as to orient the vial in an upright position.

19. The polymer vial of any one of claims 16 to 18, wherein the vial is made from an olefin polymer or copolymer, optionally cyclic olefin polymer or cyclic olefin copolymer.

20. The polymer vial of any one of claims 16 to 19, comprising a PECVD water barrier coating or layer having a water contact angle of from 80 to 180 degrees, optionally from larger than 80 degrees to less than 180 degrees, optionally from 90 degrees to 160 degrees, optionally from 100 degrees to 150 degrees, optionally from 110 degrees to 150 degrees, optionally wherein the PECVD water barrier coating or layer is deposited on an interior surface or exterior surface of the vial.

21. The polymer vial of any one of claims 16 to 20, wherein the PECVD water barrier coating or layer is applied through a process comprising: in a PECVD apparatus, supplying a water barrier coating or layer precursor to the vial and creating a plasma using the same, the water barrier coating or layer precursor comprising as least one of a saturated or unsaturated, linear or cyclic aliphatic fluorocarbon precursor having from 1 to 10, optionally 1 to 6, optionally 2 to 6 carbon atoms and from 4 to 20 fluorine atoms per molecule, optionally hexafluropropylene (C_3F_6), octafluorocyclobutane (C_4F_8), tetrafluoroethylene (C_2F_4), hexafluoroethane (C_2F_6), hexafluoropropylene (C_3F_6), octafluorocyclobutane (C_4F_8), perfluorohexane (C_6F_{14}) or perfluoro-2-methyl-2-pentene (C_6F_{12}), the water barrier coating or layer precursor further comprising a saturated or unsaturated hydrocarbon having from 1 to 6 carbon atoms, for example lower alkanes having from 1 to 4 carbon atoms, alkenes or alkynes having from 2 to 4 carbon atoms, for example acetylene (C_2H_2) or methane (CH_4), optionally acetylene (C_2H_2), a saturated or unsaturated hydrofluorocarbon having from 1 to 6 carbon atoms, or any combination thereof.

22. The polymer vial of any one of claims 16 to 21, further comprising further comprising a PECVD tri-layer coating set deposited onto an interior surface of the vial, optionally wherein the PECVD tri-layer coating set is deposited atop the PECVD water barrier layer or the PECVD water barrier layer is deposited atop the PECVD tri-layer coating set.

23. A method comprising providing a polymer vial of any one of claims 1 to 10 or 16 to 22 that is filled with a product in solution form and lyophilizing the product to render a dry powdered lyophilized form of the product within the vial.

24. A mold for making a vial, the mold comprising a first mold part and a second mold part, the first mold part and second mold part being configured to meet along a central axis to form an outer shape of a sidewall of the vial, wherein respective interior sizes and configurations of the first mold part and second mold part mirror each other, the mold further comprising a base mold configured to form a base of the vial, the base mold having a substantially flat molding surface, wherein at least 80%, optionally at least 85%, optionally at least 90%, of the molding surface of the base mold occupies a single plane, the first mold part, second mold part and base mold together defining a mold cavity when the mold is in a blowing position in which the base mold is in position relative to the first and second mold parts to form the base of the vial such that the substantially flat molding surface of the base mold is positioned entirely axially below respective molding surfaces of the first mold part and second mold part.

25. The mold of claim 24, wherein neither the first mold part nor the second mold part are configured to form any of the base of the vial.

26. The mold of claim 24 or 25, wherein the base mold is configured to form no part of the sidewall of the vial.

27. The mold of any one of claims 24 to 26, wherein each of the first mold part and second mold part include a first curved mold surface that leads to a second curved mold surface, the first curved mold surface following a radius with an imaginary center positioned in the mold cavity, the second curved mold surface following a radius with an imaginary center positioned outside the mold cavity.

28. The mold of claim 27, wherein no portion of the substantially flat molding surface of the base mold extends axially above the second curved mold surface.

29. The polymer vial of any of claims 1 to 10 or 16 to 22, wherein a lyophilized product is stored within the interior, the lyophilized product configured to be reconstituted into a liquid product.

30. The polymer vial of claim 29, wherein the lyophilized product is a biologic drug, a gene therapy or viral vector.

31. The polymer vial of claim 29, wherein the lyophilized product is at least one member selected from the group consisting of:

- INHALATION ANESTHETICS, which optionally include:

Aliflurane; Chloroform; Cyclopropane; Desflurane (Suprane); Diethyl Ether; Enflurane (Ethrane); Ethyl Chloride; Ethylene; Halothane (Fluothane); Isoflurane (Forane, Isoflo); Isopropenyl vinyl ether; Methoxyflurane; methoxyflurane; Methoxypropane; Nitrous Oxide; Roflurane; Sevoflurane (Sevorane, Ultane, Sevoflo); Teflurane; Trichloroethylene; Vinyl Ether; and Xenon;

- INJECTABLE DRUGS, which optionally include:

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 I 123 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 104mg/ml; Depo-Provera 150mg/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 I 123 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); Osmitrol Injection in Viaflex (Mannitol Injection in Viaflex Plastic Vessel); 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); 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 HCI 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); and Zyprexa Relprevv (Olanzapine Extended Release Injectable Suspension);

- LIQUID DRUGS (NON-INJECTABLE), which optionally include:

Abilify; AccuNeb (Albuterol Sulfate Inhalation Solution); Actidose Aqua (Activated Charcoal Suspension); Activated Charcoal Suspension (Actidose Aqua); Advair; Agenerase Oral Solution (Amprenavir Oral Solution); Akten (Lidocaine Hydrochloride Ophthalmic Gel); Alamast (Pemirolast Potassium Ophthalmic Solution); Albumin (Human) 5% Solution (Buminate 5%); Albuterol Sulfate Inhalation Solution; Alinia; Alocril; Alphagan; Alrex; Alvesco; Amprenavir Oral Solution; Analpram-HC; Arformoterol Tartrate Inhalation Solution (Brovana); Aristospan Injection 20 mg (Triamcinolone Hexacetonide Injectable Suspension); Asacol; Asmanex; Astepro; Astepro (Azelastine Hydrochloride Nasal Spray); Atrovent Nasal Spray (Ipratropium Bromide Nasal Spray); Atrovent Nasal Spray .06; Augmentin ES-600; Azasite (Azithromycin Ophthalmic Solution); Azelaic Acid (Finacea Gel); Azelastine Hydrochloride Nasal Spray (Astepro); Azelex (Azelaic Acid Cream); Azopt (Brinzolamide Ophthalmic Suspension); Bacteriostatic Saline; Balanced Salt; Bepotastine; Bactroban Nasal; Bactroban; Beclovent; Benzac W; Betimol; Betoptic S; Bepreve; Bimatoprost Ophthalmic Solution; Bleph 10 (Sulfacetamide Sodium Ophthalmic Solution 10%); Brinzolamide Ophthalmic Suspension (Azopt); Bromfenac Ophthalmic Solution (Xibrom); Bromhist; Brovana (Arformoterol Tartrate Inhalation Solution); Budesonide Inhalation Suspension (Pulmicort Respules); Cambia (Diclofenac Potassium for Oral Solution); Capex; Carac; Carboxine-PSE; Carnitor; Cayston (Aztreonam for Inhalation Solution); Cellcept; Centany; Cerumenex; Ciloxan Ophthalmic Solution (Ciprofloxacin HCL Ophthalmic Solution); Ciprodex; Ciprofloxacin HCL Ophthalmic Solution (Ciloxan Ophthalmic Solution); Clemastine Fumarate Syrup (Clemastine Fumarate Syrup); CoLyte (PEG Electrolytes Solution); Combiven; Comtan; Condylox; Cordran; Cortisporin Ophthalmic Suspension; Cortisporin Otic Suspension; Cromolyn Sodium Inhalation Solution (Intal Nebulizer Solution); Cromolyn Sodium Ophthalmic Solution (Opticrom); Crystalline Amino Acid Solution with Electrolytes (Aminosyn Electrolytes); Cutivate; Cuvposa (Glycopyrrolate Oral Solution); Cyanocobalamin (CaloMist Nasal Spray); Cyclosporine Oral Solution (Gengraf Oral Solution); Cyclogyl; Cysview (Hexaminolevulinate Hydrochloride Intravesical Solution); DermOtic Oil (Fluocinolone Acetonide Oil Ear Drops); Desmopressin Acetate Nasal Spray; DDAVP; Derma-Smoothe/FS; Dexamethasone Intensol; Dianeal Low Calcium; Dianeal PD; Diclofenac Potassium for

Oral Solution (Cambia); Didanosine Pediatric Powder for Oral Solution (Videx); Differin; Dilantin 125 (Phenytoin Oral Suspension); Ditropan; Dorzolamide Hydrochloride Ophthalmic Solution (Trusopt); Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution (Cosopt); Dovonex Scalp (Calcipotriene Solution); Doxycycline Calcium Oral Suspension (Vibramycin Oral); Efudex; Elaprase (Idursulfase Solution); Elestat (Epinastine HCl Ophthalmic Solution); Elocon; Epinastine HCl Ophthalmic Solution (Elestat); Epivir HBV; Epogen (Epoetin alfa); Erythromycin Topical Solution 1.5% (Staticin); Ethiodol (Ethiodized Oil); Ethosuximide Oral Solution (Zarontin Oral Solution); Eurax; Extraneal (Icodextrin Peritoneal Dialysis Solution); Felbatol; Feridex I.V. (Ferumoxides Injectable Solution); Flovent; Floxin Otic (Ofloxacin Otic Solution); Flo- Pred (Prednisolone Acetate Oral Suspension); Fluoroplex; Flunisolide Nasal Solution (Flunisolide Nasal Spray .025%); Fluorometholone Ophthalmic Suspension (FML); Flurbiprofen Sodium Ophthalmic Solution (Ocufen); FML; Foradil; Formoterol Fumarate Inhalation Solution (Perforomist); Fosamax; Furadantin (Nitrofurantoin Oral Suspension); Furoxone; Gammagard Liquid (Immune Globulin Intravenous (Human) 10%); Gantrisin (Acetyl Sulfisoxazole Pediatric Suspension); Gatifloxacin Ophthalmic Solution (Zymar); Gengraf Oral Solution (Cyclosporine Oral Solution); Glycopyrrolate Oral Solution (Cuvposa); Halcinonide Topical Solution (Halog Solution); Halog Solution (Halcinonide Topical Solution); HEP-LOCK U/P (Preservative-Free Heparin Lock Flush Solution); Heparin Lock Flush Solution (Hepflush 10); Hexaminolevulinate Hydrochloride Intravesical Solution (Cysview); Hydrocodone Bitartrate and Acetaminophen Oral Solution (Lortab Elixir); Hydroquinone 3% Topical Solution (Melquin-3 Topical Solution); IAP Antagonist; Isopto; Ipratropium Bromide Nasal Spray (Atrovent Nasal Spray); Itraconazole Oral Solution (Sporanox Oral Solution); Ketorolac Tromethamine Ophthalmic Solution (Acular LS); Kaletra; Lanoxin; Lexiva; Leuprolide Acetate for Depot Suspension (Lupron Depot 11.25 mg); Levobetaxolol Hydrochloride Ophthalmic Suspension (Betaxon); Levocarnitine Tablets, Oral Solution, Sugar-Free (Carnitor); Levofloxacin Ophthalmic Solution 0.5% (Quixin); Lidocaine HCl Sterile Solution (Xylocaine MPF Sterile Solution); Lok Pak (Heparin Lock Flush Solution); Lorazepam Intensol; Lortab Elixir (Hydrocodone Bitartrate and Acetaminophen Oral Solution); Lotemax (Loteprednol Etabonate Ophthalmic Suspension); Loteprednol Etabonate Ophthalmic Suspension (Alrex); Low Calcium Peritoneal Dialysis Solutions (Dianeal Low Calcium); Lumigan (Bimatoprost Ophthalmic Solution 0.03% for Glaucoma); Lupron Depot 11.25 mg (Leuprolide Acetate for Depot Suspension);

Megestrol Acetate Oral Suspension (Megestrol Acetate Oral Suspension); MEK Inhibitor; Mepron; Mesnex; Mestinon; Mesalamine Rectal Suspension Enema (Rowasa); Melquin-3 Topical Solution (Hydroquinone 3% Topical Solution); MetMab; Methyldopate Hcl (Methyldopate Hydrochloride Injection, Solution); Methylin Oral Solution (Methylphenidate HCl Oral Solution 5 mg/5 mL and 10 mg/5 mL); Methylprednisolone Acetate Injectable Suspension (Depo Medrol); Methylphenidate HCl Oral Solution 5 mg/5 mL and 10 mg/5 mL (Methylin Oral Solution); Methylprednisolone sodium succinate (Solu Medrol); Metipranolol Ophthalmic Solution (Optipranolol); Migranal; Miochol-E (Acetylcholine Chloride Intraocular Solution); Micro-K for Liquid Suspension (Potassium Chloride Extended Release Formulation for Liquid Suspension); Minocin (Minocycline Hydrochloride Oral Suspension); Nasacort; Neomycin and Polymyxin B Sulfates and Hydrocortisone; Nepafenac Ophthalmic Suspension (Nevanac); Nevanac (Nepafenac Ophthalmic Suspension); Nitrofurantoin Oral Suspension (Furadantin); Noxafil (Posaconazole Oral Suspension); Nystatin (oral) (Nystatin Oral Suspension); Nystatin Oral Suspension (Nystatin (oral)); Ocufen (Flurbiprofen Sodium Ophthalmic Solution); Ofloxacin Ophthalmic Solution (Ofloxacin Ophthalmic Solution); Ofloxacin Otic Solution (Floxin Otic); Olopatadine Hydrochloride Ophthalmic Solution (Pataday); Opticrom (Cromolyn Sodium Ophthalmic Solution); Optipranolol (Metipranolol Ophthalmic Solution); Patanol; Pediapred; PerioGard; Phenytoin Oral Suspension (Dilantin 125); Phisohex; Posaconazole Oral Suspension (Noxafil); Potassium Chloride Extended Release Formulation for Liquid Suspension (Micro-K for Liquid Suspension); Pataday (Olopatadine Hydrochloride Ophthalmic Solution); Patanase Nasal Spray (Olopatadine Hydrochloride Nasal Spray); PEG Electrolytes Solution (CoLyte); Pemirolast Potassium Ophthalmic Solution (Alamast); Penlac (Ciclopirox Topical Solution); PENNSAID (Diclofenac Sodium Topical Solution); Perforomist (Formoterol Fumarate Inhalation Solution); Peritoneal Dialysis Solution; Phenylephrine Hydrochloride Ophthalmic Solution (Neo-Synephrine); Phospholine Iodide (Echothiophate Iodide for Ophthalmic Solution); Podofilox (Podofilox Topical Solution); Pred Forte (Prednisolone Acetate Ophthalmic Suspension); Pralatrexate Solution for Intravenous Injection (Folotyn); Pred Mild; Prednisone Intensol; Prednisolone Acetate Ophthalmic Suspension (Pred Forte); Prevacid; PrismaSol Solution (Sterile Hemofiltration Hemodiafiltration Solution); ProAir; Proglycem; ProHance (Gadoteridol Injection Solution); Proparacaine Hydrochloride Ophthalmic Solution (Alcaine); Propine; Pulmicort; Pulmozyme; Quixin (Levofloxacin Ophthalmic Solution 0.5%); QVAR; Rapamune; Rebetol;

Relacon-HC; Rotarix (Rotavirus Vaccine, Live, Oral Suspension); Rotavirus Vaccine, Live, Oral Suspension (Rotarix); Rowasa (Mesalamine Rectal Suspension Enema); Sabril (Vigabatrin Oral Solution); Sacrosidase Oral Solution (Sucraid); Sandimmune; Sepra; Serevent Diskus; Solu Cortef (Hydrocortisone Sodium Succinate); Solu Medrol (Methylprednisolone sodium succinate); Spiriva; Sporanox Oral Solution (Itraconazole Oral Solution); Staticin (Erythromycin Topical Solution 1.5%); Stalevo; Starlix; Sterile Hemofiltration Hemodiafiltration Solution (PrismaSol Solution); Stimate; Sucralfate (Carafate Suspension); Sulfacetamide Sodium Ophthalmic Solution 10% (Bleph 10); Synarel Nasal Solution (Nafarelin Acetate Nasal Solution for Endometriosis); Taclonex Scalp (Calcipotriene and Betamethasone Dipropionate Topical Suspension); Tamiflu; Tobi; TobraDex; Tobradex ST (Tobramycin / Dexamethasone Ophthalmic Suspension 0.3%/0.05%); Tobramycin / Dexamethasone Ophthalmic Suspension 0.3%/0.05% (Tobradex ST); Timolol; Timoptic; Travatan Z; Treprostinil Inhalation Solution (Tyvaso); Trusopt (Dorzolamide Hydrochloride Ophthalmic Solution); Tyvaso (Treprostinil Inhalation Solution); Ventolin; Vfend; Vibramycin Oral (Doxycycline Calcium Oral Suspension); Videx (Didanosine Pediatric Powder for Oral Solution); Vigabatrin Oral Solution (Sabril); Viokase; Viracept; Viramune; Vitamin K1 (Fluid Colloidal Solution of Vitamin K1); Voltaren Ophthalmic (Diclofenac Sodium Ophthalmic Solution); Zarontin Oral Solution (Ethosuximide Oral Solution); Ziagen; Zyvox; Zymar (Gatifloxacin Ophthalmic Solution); and Zymaxid (Gatifloxacin Ophthalmic Solution);

- DRUG CLASSES, which optionally include:

5-alpha-reductase inhibitors; 5-aminosalicylates; 5HT3 receptor antagonists; adamantane antivirals; adrenal cortical steroids; adrenal corticosteroid inhibitors; adrenergic bronchodilators; agents for hypertensive emergencies; agents for pulmonary hypertension; aldosterone receptor antagonists; alkylating agents; alpha-adrenoreceptor antagonists; alpha-glucosidase inhibitors; alternative medicines; amebicides; aminoglycosides; aminopenicillins; aminosalicylates; amylin analogs; Analgesic Combinations; Analgesics; androgens and anabolic steroids; angiotensin converting enzyme inhibitors; angiotensin II inhibitors; anorectal preparations; anorexiants; antacids; anthelmintics; anti-angiogenic ophthalmic agents; anti-CTLA-4 monoclonal antibodies; anti-infectives; antiadrenergic agents, centrally acting; antiadrenergic agents, peripherally acting; antiandrogens; antianginal agents; antiarrhythmic agents; antiasthmatic combinations; antibiotics/antineoplastics; anticholinergic antiemetics; anticholinergic antiparkinson agents;

anticholinergic bronchodilators; anticholinergic chronotropic agents; anticholinergics/antispasmodics; anticoagulants; anticonvulsants; antidepressants; antidiabetic agents; antidiabetic combinations; antidiarrheals; antidiuretic hormones; antidotes; antiemetic/antivertigo agents; antifungals; antigonadotropic agents; antigout agents; antihistamines; antihyperlipidemic agents; antihyperlipidemic combinations; antihypertensive combinations; antihyperuricemic agents; antimalarial agents; antimalarial combinations; antimalarial quinolines; antimetabolites; antimigraine agents; antineoplastic detoxifying agents; antineoplastic interferons; antineoplastic monoclonal antibodies; antineoplastics; antiparkinson agents; antiplatelet agents; antipseudomonal penicillins; antipsoriatics; antipsychotics; antirheumatics; antiseptic and germicides; antithyroid agents; antitoxins and antivenins; antituberculosis agents; antituberculosis combinations; antitussives; antiviral agents; antiviral combinations; antiviral interferons; anxiolytics, sedatives, and hypnotics; aromatase inhibitors; atypical antipsychotics; azole antifungals; bacterial vaccines; barbiturate anticonvulsants; barbiturates; BCR-ABL tyrosine kinase inhibitors; benzodiazepine anticonvulsants; benzodiazepines; beta-adrenergic blocking agents; beta-lactamase inhibitors; bile acid sequestrants; biologicals; bisphosphonates; bone resorption inhibitors; bronchodilator combinations; bronchodilators; calcitonin; calcium channel blocking agents; carbamate anticonvulsants; carbapenems; carbonic anhydrase inhibitor anticonvulsants; carbonic anhydrase inhibitors; cardiac stressing agents; cardioselective beta blockers; cardiovascular agents; catecholamines; CD20 monoclonal antibodies; CD33 monoclonal antibodies; CD52 monoclonal antibodies; central nervous system agents; cephalosporins; cerumenolytics; chelating agents; chemokine receptor antagonist; chloride channel activators; cholesterol absorption inhibitors; cholinergic agonists; cholinergic muscle stimulants; cholinesterase inhibitors; CNS stimulants; coagulation modifiers; colony stimulating factors; contraceptives; corticotropin; coumarins and indandiones; cox-2 inhibitors; decongestants; dermatological agents; diagnostic radiopharmaceuticals; dibenzazepine anticonvulsants; digestive enzymes; dipeptidyl peptidase 4 inhibitors; diuretics; dopaminergic antiparkinsonism agents; drugs used in alcohol dependence; echinocandins; EGFR inhibitors; estrogen receptor antagonists; estrogens; expectorants; factor Xa inhibitors; fatty acid derivative anticonvulsants; fibric acid derivatives; first generation cephalosporins; fourth generation cephalosporins; functional bowel disorder agents; gallstone solubilizing agents; gamma-aminobutyric acid analogs; gamma-aminobutyric acid reuptake

inhibitors; gamma-aminobutyric acid transaminase inhibitors; gastrointestinal agents; general anesthetics; genitourinary tract agents; GI stimulants; glucocorticoids; glucose elevating agents; glycopeptide antibiotics; glycoprotein platelet inhibitors; glycylcyclines; gonadotropin releasing hormones; gonadotropin-releasing hormone antagonists; gonadotropins; group I antiarrhythmics; group II antiarrhythmics; group III antiarrhythmics; group IV antiarrhythmics; group V antiarrhythmics; growth hormone receptor blockers; growth hormones; H. pylori eradication agents; H2 antagonists; hematopoietic stem cell mobilizer; heparin antagonists; heparins; HER2 inhibitors; herbal products; histone deacetylase inhibitors; hormone replacement therapy; hormones; hormones/antineoplastics; hydantoin anticonvulsants; illicit (street) drugs; immune globulins; immunologic agents; immunosuppressive agents; impotence agents; in vivo diagnostic biologicals; incretin mimetics; inhaled anti-infectives; inhaled corticosteroids; inotropic agents; insulin; insulin-like growth factor; integrase strand transfer inhibitor; interferons; intravenous nutritional products; iodinated contrast media; ionic iodinated contrast media; iron products; ketolides; laxatives; leprostatics; leukotriene modifiers; lincomycin derivatives; lipoglycopeptides; local injectable anesthetics; loop diuretics; lung surfactants; lymphatic staining agents; lysosomal enzymes; macrolide derivatives; macrolides; magnetic resonance imaging contrast media; mast cell stabilizers; medical gas; meglitinides; metabolic agents; methylxanthines; mineralocorticoids; minerals and electrolytes; miscellaneous agents; miscellaneous analgesics; miscellaneous antibiotics; miscellaneous anticonvulsants; miscellaneous antidepressants; miscellaneous antidiabetic agents; miscellaneous antiemetics; miscellaneous antifungals; miscellaneous antihyperlipidemic agents; miscellaneous antimalarials; miscellaneous antineoplastics; miscellaneous antiparkinson agents; miscellaneous antipsychotic agents; miscellaneous antituberculosis agents; miscellaneous antivirals; miscellaneous anxiolytics, sedatives and hypnotics; miscellaneous biologicals; miscellaneous bone resorption inhibitors; miscellaneous cardiovascular agents; miscellaneous central nervous system agents; miscellaneous coagulation modifiers; miscellaneous diuretics; miscellaneous genitourinary tract agents; miscellaneous GI agents; miscellaneous hormones; miscellaneous metabolic agents; miscellaneous ophthalmic agents; miscellaneous otic agents; miscellaneous respiratory agents; miscellaneous sex hormones; miscellaneous topical agents; miscellaneous uncategorized agents; miscellaneous vaginal agents; mitotic inhibitors; monoamine oxidase inhibitors; monoclonal antibodies; mouth and throat products; mTOR inhibitors; mTOR kinase inhibitors; mucolytics;

multikinase inhibitors; muscle relaxants; mydriatics; narcotic analgesic combinations; narcotic analgesics; nasal anti-infectives; nasal antihistamines and decongestants; nasal lubricants and irrigations; nasal preparations; nasal steroids; natural penicillins; neuraminidase inhibitors; neuromuscular blocking agents; next generation cephalosporins; nicotinic acid derivatives; nitrates; NNRTIs; non- cardioselective beta blockers; non-iodinated contrast media; non-ionic iodinated contrast media; non-sulfonylureas; nonsteroidal anti-inflammatory agents; norepinephrine reuptake inhibitors; norepinephrine-dopamine reuptake inhibitors; nucleoside reverse transcriptase inhibitors (NRTIs); nutraceutical products; nutritional products; ophthalmic anesthetics; ophthalmic anti-infectives; ophthalmic anti- inflammatory agents; ophthalmic antihistamines and decongestants; ophthalmic diagnostic agents; ophthalmic glaucoma agents; ophthalmic lubricants and irrigations; ophthalmic preparations; ophthalmic steroids; ophthalmic steroids with anti-infectives; ophthalmic surgical agents; oral nutritional supplements; otic anesthetics; otic anti- infectives; otic preparations; otic steroids; otic steroids with anti-infectives; oxazolidinedione anticonvulsants; parathyroid hormone and analogs; penicillinase resistant penicillins; penicillins; peripheral opioid receptor antagonists; peripheral vasodilators; peripherally acting antiobesity agents; phenothiazine antiemetics; phenothiazine antipsychotics; phenylpiperazine antidepressants; plasma expanders; platelet aggregation inhibitors; platelet-stimulating agents; polyenes; potassium-sparing diuretics; probiotics; progesterone receptor modulators; progestins; prolactin inhibitors; prostaglandin D2 antagonists; protease inhibitors; proton pump inhibitors; psoralens; psychotherapeutic agents; psychotherapeutic combinations; purine nucleosides; pyrrolidine anticonvulsants; quinolones; radiocontrast agents; radiologic adjuncts; radiologic agents; radiologic conjugating agents; radiopharmaceuticals; RANK ligand inhibitors; recombinant human erythropoietins; renin inhibitors; respiratory agents; respiratory inhalant products; rifamycin derivatives; salicylates; sclerosing agents; second generation cephalosporins; selective estrogen receptor modulators; selective serotonin reuptake inhibitors; serotonin-norepinephrine reuptake inhibitors; serotoninergic neuroenteric modulators; sex hormone combinations; sex hormones; skeletal muscle relaxant combinations; skeletal muscle relaxants; smoking cessation agents; somatostatin and somatostatin analogs; spermicides; statins; sterile irrigating solutions; streptomyces derivatives; succinimide anticonvulsants; sulfonamides; sulfonylureas; synthetic ovulation stimulants; tetracyclic antidepressants; tetracyclines; therapeutic radiopharmaceuticals; thiazide diuretics;

thiazolidinediones; thioxanthenes; third generation cephalosporins; thrombin inhibitors; thrombolytics; thyroid drugs; tocolytic agents; topical acne agents; topical agents; topical anesthetics; topical anti- infectives; topical antibiotics; topical antifungals; topical antihistamines; topical antipsoriatics; topical antivirals; topical astringents; topical debriding agents; topical depigmenting agents; topical emollients; topical keratolytics; topical steroids; topical steroids with anti-infectives; toxoids; triazine anticonvulsants; tricyclic antidepressants; trifunctional monoclonal antibodies; tumor necrosis factor (TNF) inhibitors; tyrosine kinase inhibitors; ultrasound contrast media; upper respiratory combinations; urea anticonvulsants; urinary anti-infectives; urinary antispasmodics; urinary pH modifiers; uterotonic agents; vaccine; vaccine combinations; vaginal anti-infectives; vaginal preparations; vasodilators; vasopressin antagonists; vasopressors; VEGF/VEGFR inhibitors; viral vaccines; viscosupplementation agents; vitamin and mineral combinations; and vitamins;

and

- DIAGNOSTIC TESTS, which optionally include:

17-Hydroxyprogesterone; ACE (Angiotensin I converting enzyme); Acetaminophen; Acid phosphatase; ACTH; Activated clotting time; Activated protein C resistance; Adrenocorticotropic hormone (ACTH); Alanine aminotransferase (ALT); Albumin; Aldolase; Aldosterone; Alkaline phosphatase; Alkaline phosphatase (ALP); Alpha1- antitrypsin; Alpha-fetoprotein; Alpha-fetoprotien; Ammonia levels; Amylase; ANA (antinuclear antbodies); ANA (antinuclear antibodies); Angiotensin-converting enzyme (ACE); Anion gap; Anticardiolipin antibody; Anticardiolipin antivbodies (ACA); Anti- centromere antibody; Antidiuretic hormone; Anti-DNA; Anti-Dnase-B; Anti-Gliadin antibody; Anti-glomerular basement membrane antibody; Anti-HBc (Hepatitis B core antibodies; Anti-HBs (Hepatitis B surface antibody; Antiphospholipid antibody; Anti-RNA polymerase; Anti-Smith (Sm) antibodies; Anti-Smooth Muscle antibody; Antistreptolysin O (ASO); Antithrombin III; Anti-Xa activity; Anti-Xa assay; Apolipoproteins; Arsenic; Aspartate aminotransferase (AST); B12; Basophil; Beta-2-Microglobulin; Beta- hydroxybutyrate; B-HCG; Bilirubin; Bilirubin, direct; Bilirubin, indirect; Bilirubin, total; Bleeding time; Blood gases (arterial); Blood urea nitrogen (BUN); BUN; BUN (blood urea nitrogen); CA 125; CA 15-3; CA 19-9; Calcitonin; Calcium; Calcium (ionized); Carbon monoxide (CO); Carcinoembryonic antigen (CEA); CBC; CEA; CEA (carcinoembryonic antigen); Ceruloplasmin; CH50Chloride; Cholesterol; Cholesterol, HDL; Clot lysis time; Clot retraction time; CMP; CO2; Cold agglutinins; Complement

C3; Copper; Corticotrophin releasing hormone (CRH) stimulation test; Cortisol; Cortrosyn stimulation test; C-peptide; CPK (Total); CPK-MB; C-reactive protein; Creatinine; Creatinine kinase (CK); Cryoglobulins; DAT (Direct antiglobulin test); D-Dimer; Dexamethasone suppression test; DHEA-S; Dilute Russell viper venom; Elliptocytes; Eosinophil; Erythrocyte sedimentation rate (ESR); Estradiol; Estriol; Ethanol; Ethylene glycol; Euglobulin lysis; Factor V Leiden; Factor VIII inhibitor; Factor VIII level; Ferritin; Fibrin split products; Fibrinogen; Folate; Folate (serum; Fractional excretion of sodium (FENA); FSH (follicle stimulating factor); FTA-ABS; Gamma glutamyl transferase (GGT); Gastrin; GGTP (Gamma glutamyl transferase); Glucose; Growth hormone; Haptoglobin; HBeAg (Hepatitis Be antigen); HBs-Ag (Hepatitis B surface antigen); Helicobacter pylori; Hematocrit; Hematocrit (HCT); Hemoglobin; Hemoglobin A1C; Hemoglobin electrophoresis; Hepatitis A antibodies; Hepatitis C antibodies; IAT (Indirect antiglobulin test); Immunofixation (IFE); Iron; Lactate dehydrogenase (LDH); Lactic acid (lactate); LDH; LH (Leutinizing hormone; Lipase; Lupus anticoagulant; Lymphocyte; Magnesium; MCH (mean corpuscular hemoglobin; MCHC (mean corpuscular hemoglobin concentration); MCV (mean corpuscular volume); Methylmalonate; Monocyte; MPV (mean platelet volume); Myoglobin; Neutrophil; Parathyroid hormone (PTH); Phosphorus; Platelets (plt); Potassium; Prealbumin; Prolactin; Prostate specific antigen (PSA); Protein C; Protein S; PSA (prostate specific antigen); PT (Prothrombin time); PTT (Partial thromboplastin time); RDW (red cell distribution width); Renin; Rennin; Reticulocyte count; reticulocytes; Rheumatoid factor (RF); Sed Rate; Serum glutamic-pyruvic transaminase (SGPT; Serum protein electrophoresis (SPEP); Sodium; T3-resin uptake (T3RU); T4, Free; Thrombin time; Thyroid stimulating hormone (TSH); Thyroxine (T4); Total iron binding capacity (TIBC); Total protein; Transferrin; Transferrin saturation; Triglyceride (TG); Troponin; Uric acid; Vitamin B12; White blood cells (WBC); and Widal test.

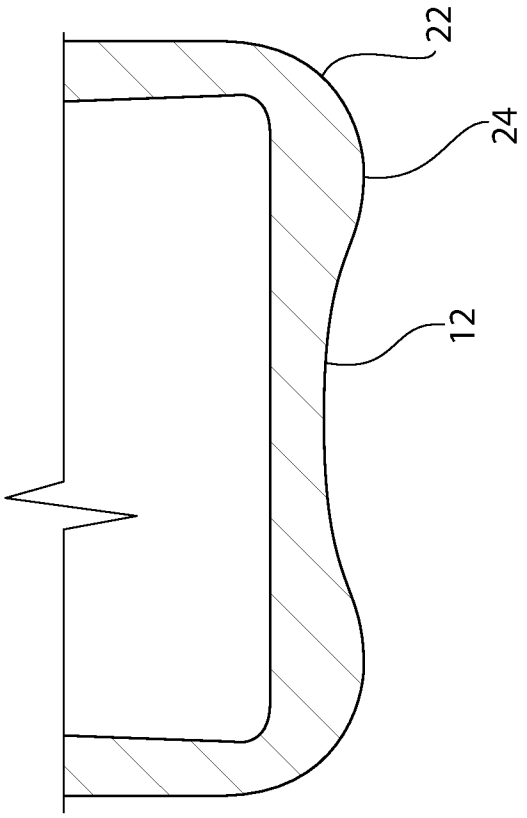


FIG. 1A
(PRIOR ART)

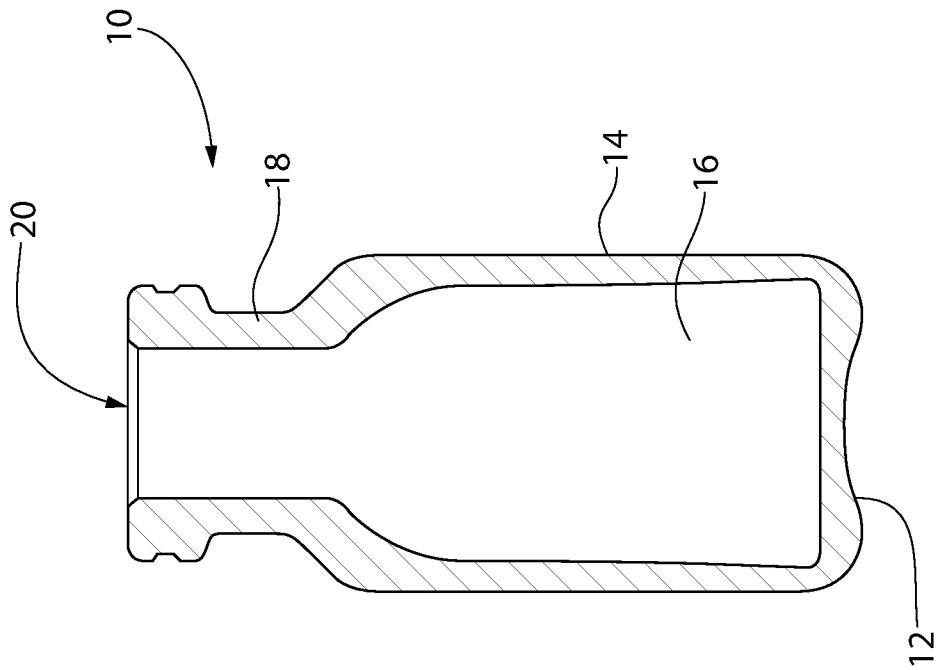


FIG. 1
(PRIOR ART)

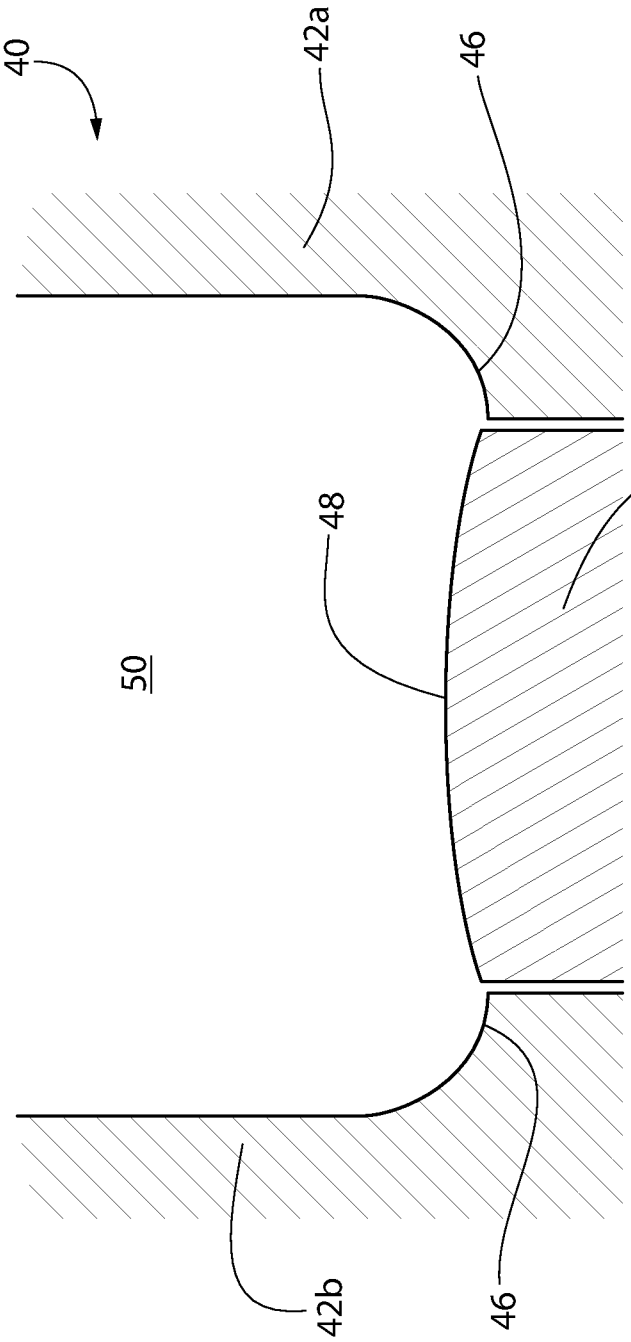


FIG. 2
(PRIOR ART)

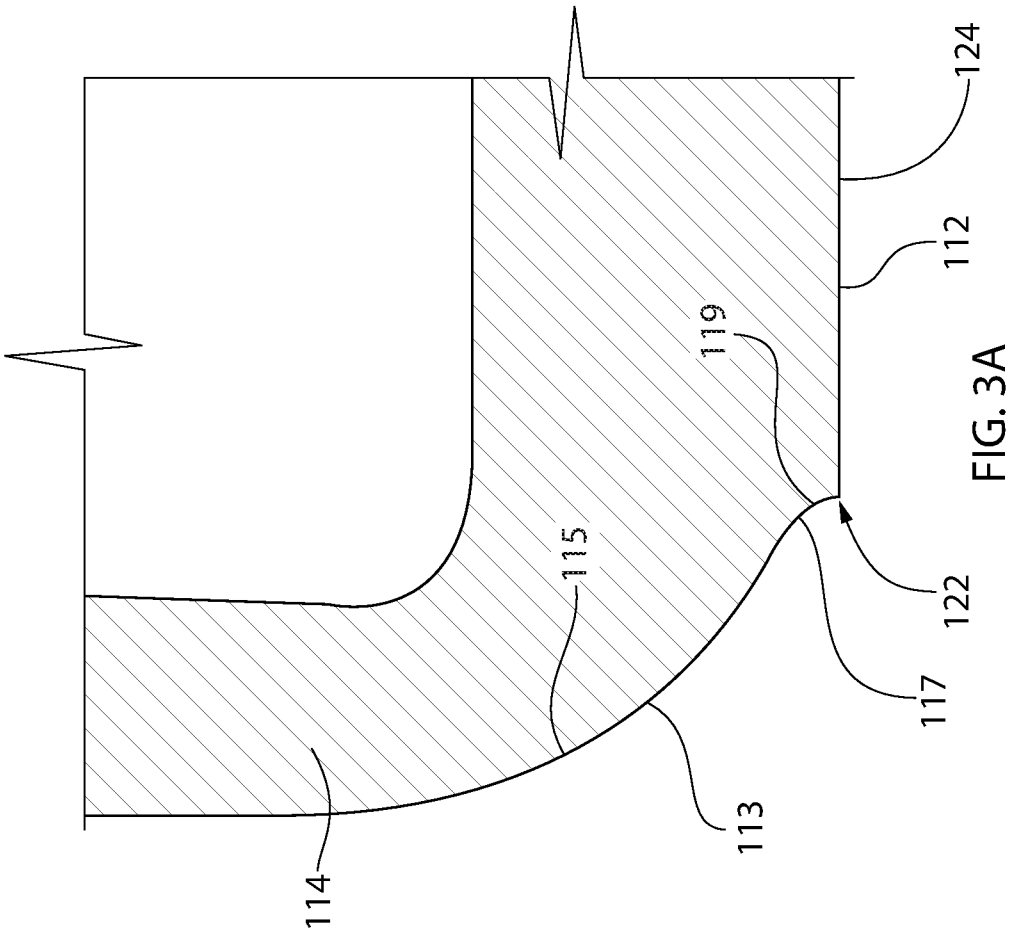


FIG. 3A

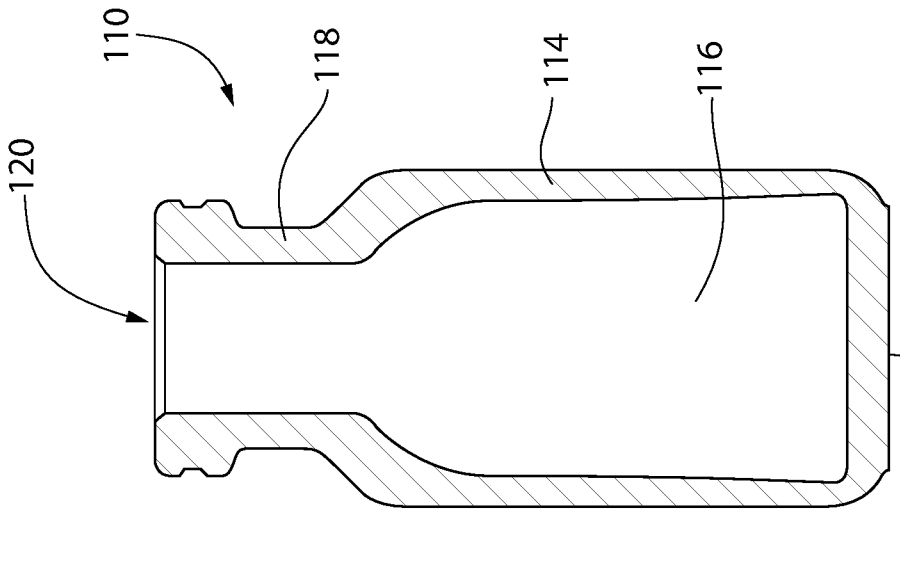


FIG. 3

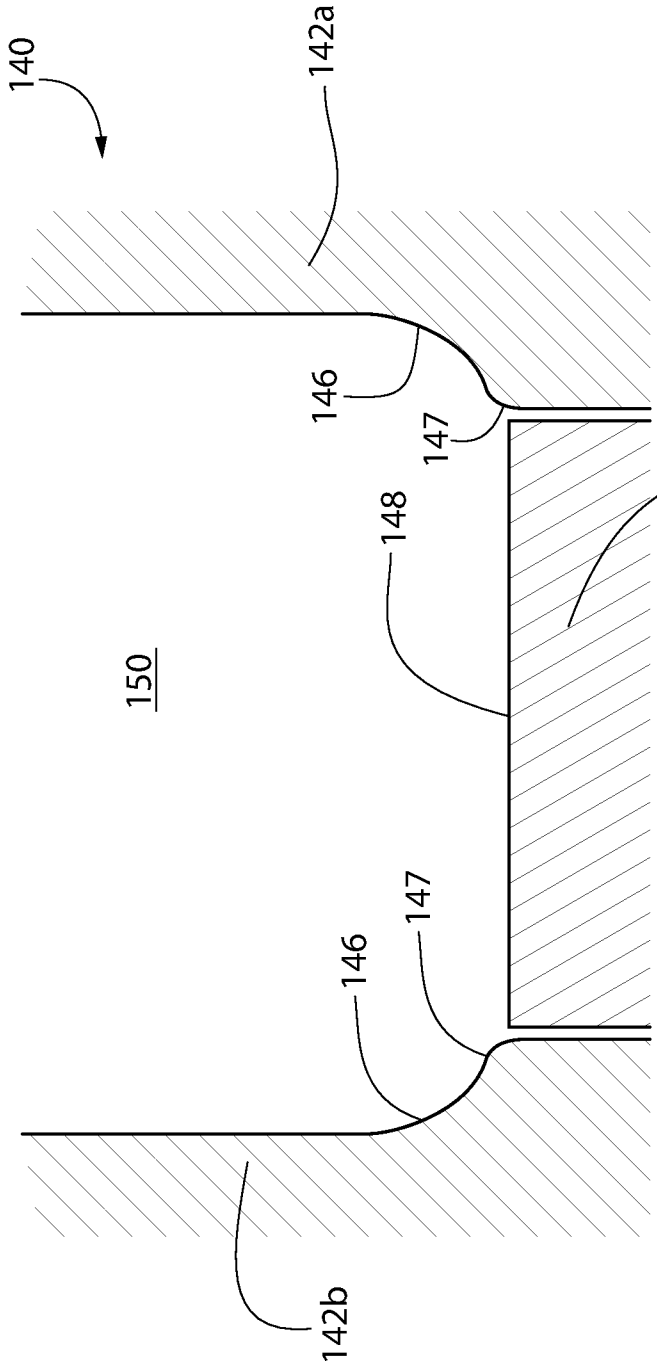


FIG. 4

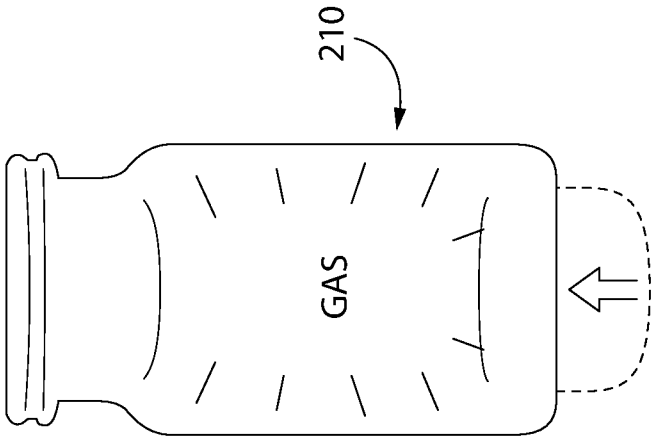


FIG. 5C

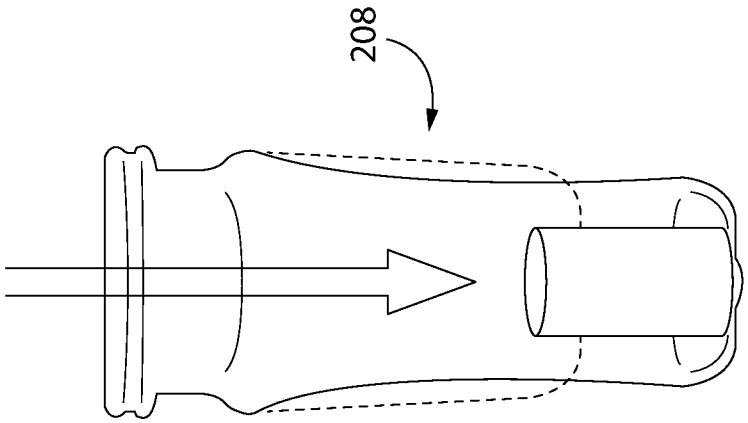


FIG. 5B

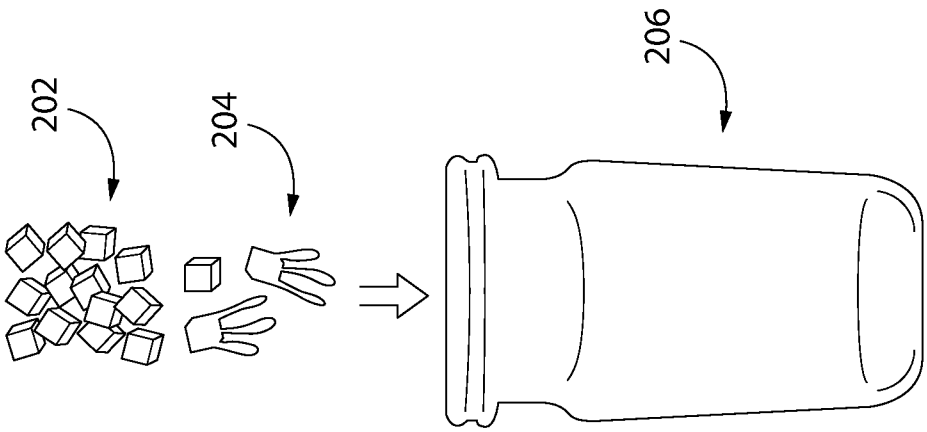


FIG. 5A

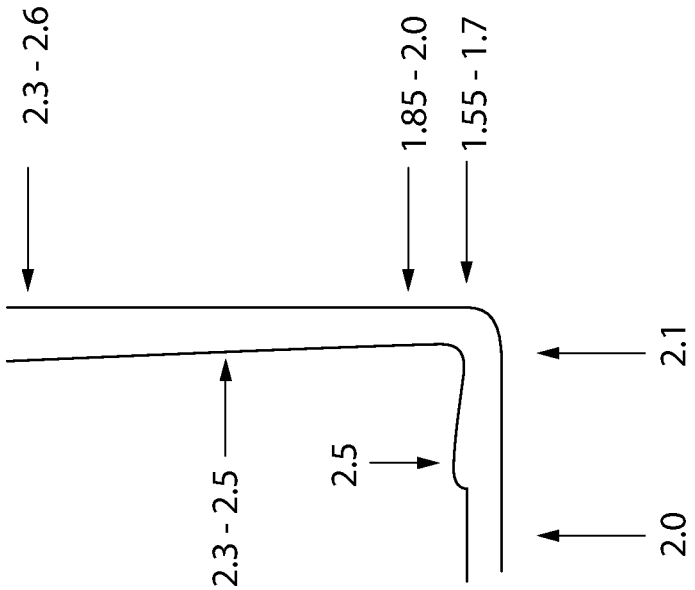


FIG. 6B

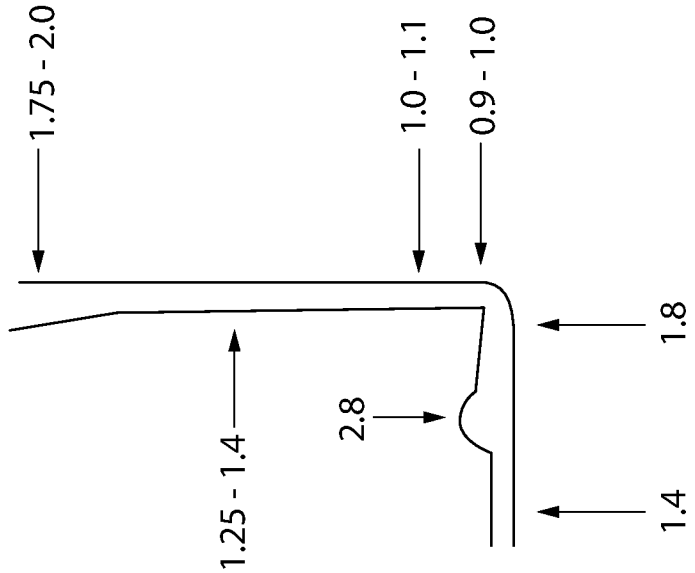


FIG. 6A

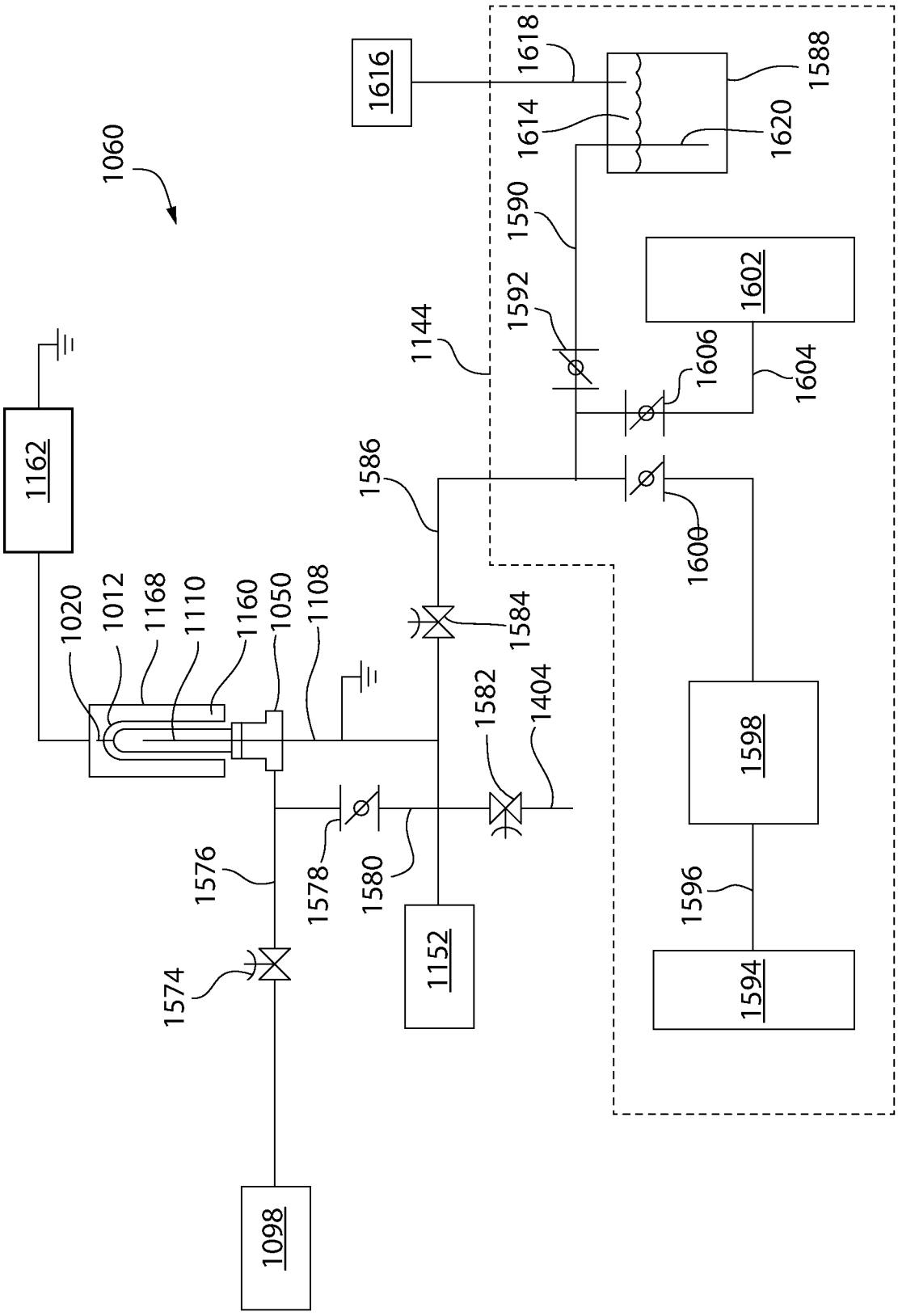

1060
1162
1020
1012
1168
1110
1160
1050
1108
1098
1574
1576
1578
1580
1152
1582
1404
1584
1586
1144
1590
1592
1600
1606
1602
1604
1598
1596
1594
1616
1618
1614
1620
1588

FIG. 7

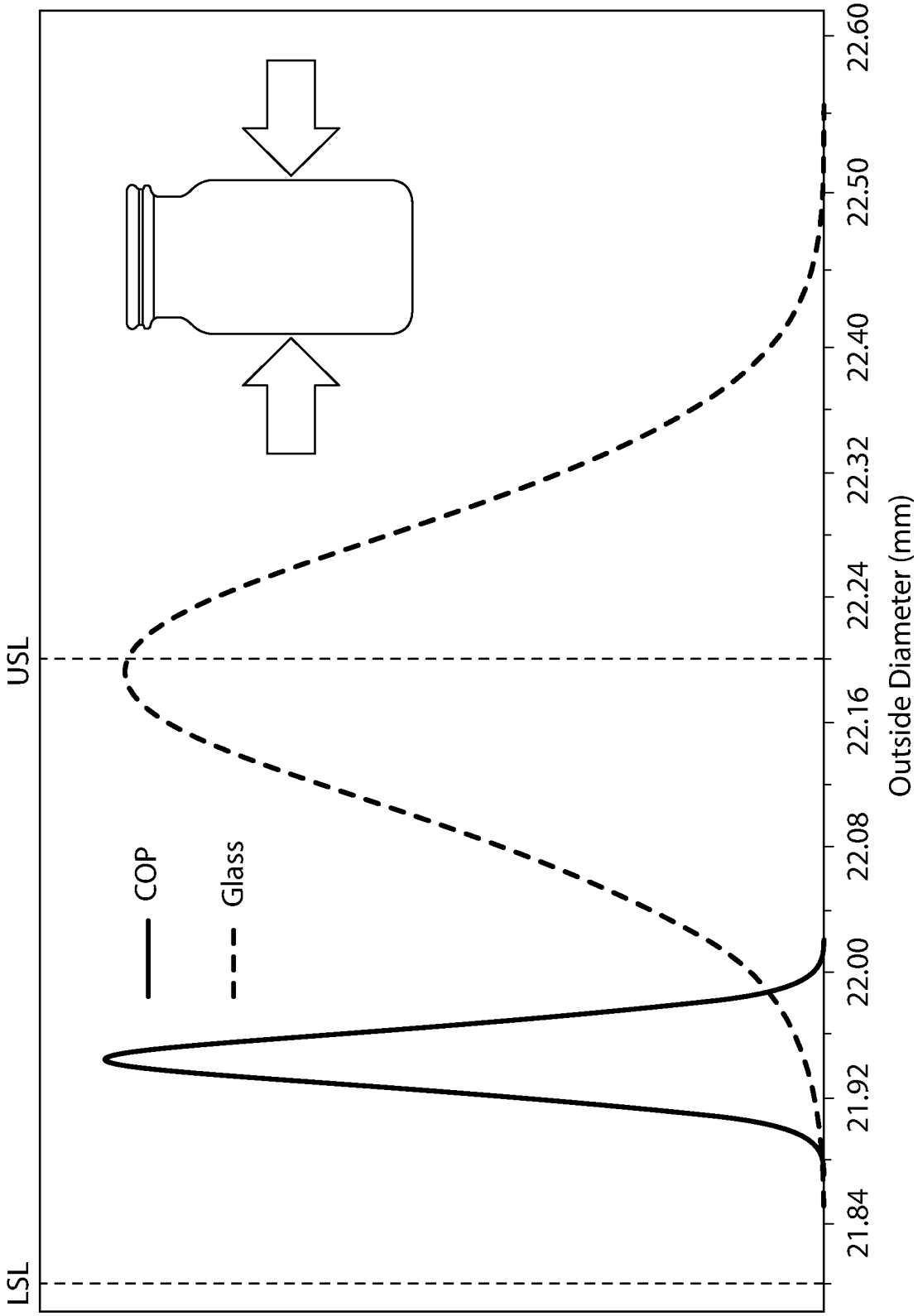

USL
LSL
COP
Glass
21.84
21.92
22.00
22.08
22.16
22.24
22.32
22.40
22.50
22.60
Outside Diameter (mm)

FIG. 8

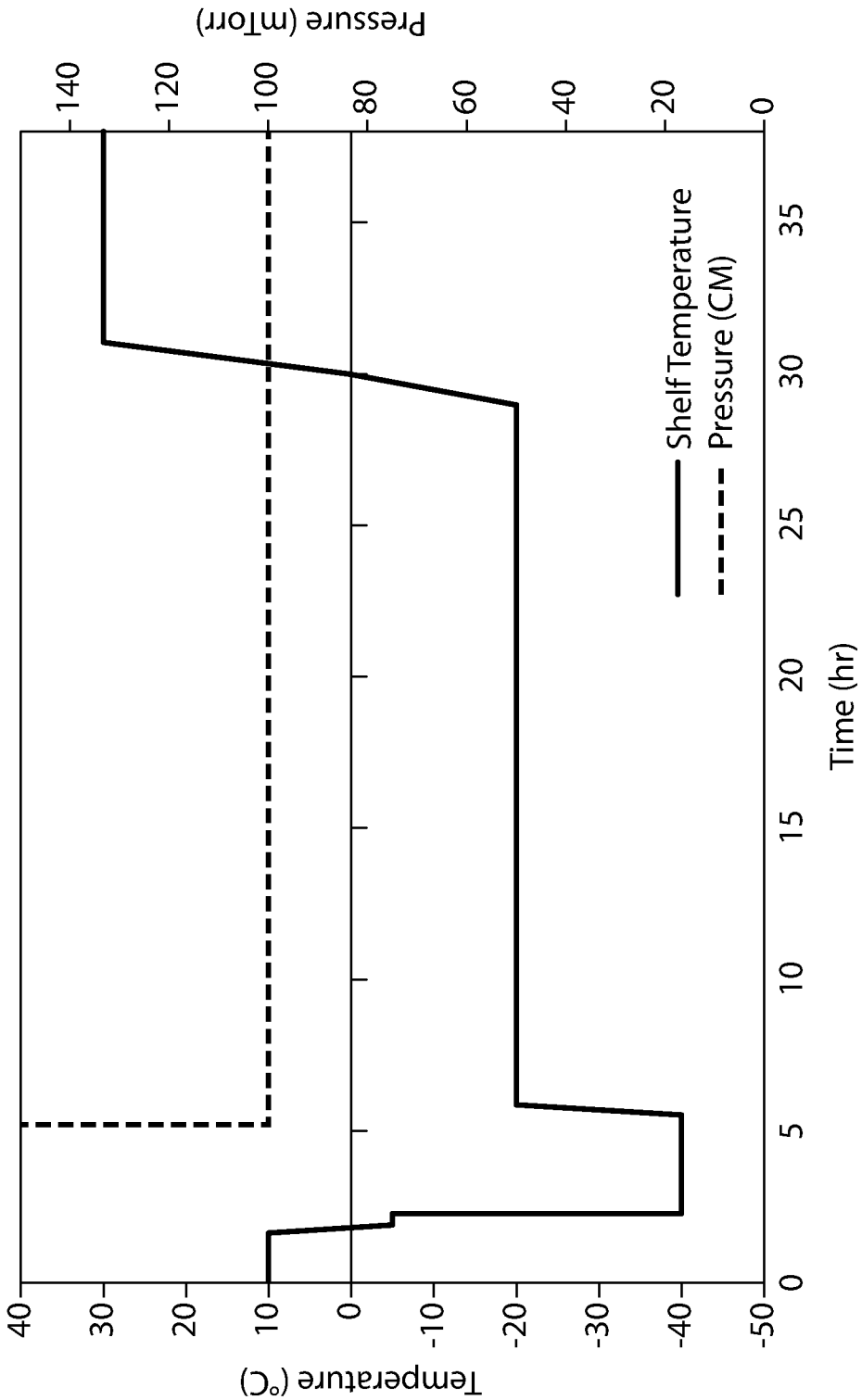

Pressure (mTorr)
140
120
100
80
60
40
20
0
Temperature (°C)
40
30
20
10
0
-10
-20
-30
-40
-50
0
5
10
15
20
25
30
35
Time (hr)
Shelf Temperature
Pressure (CM)

FIG. 9